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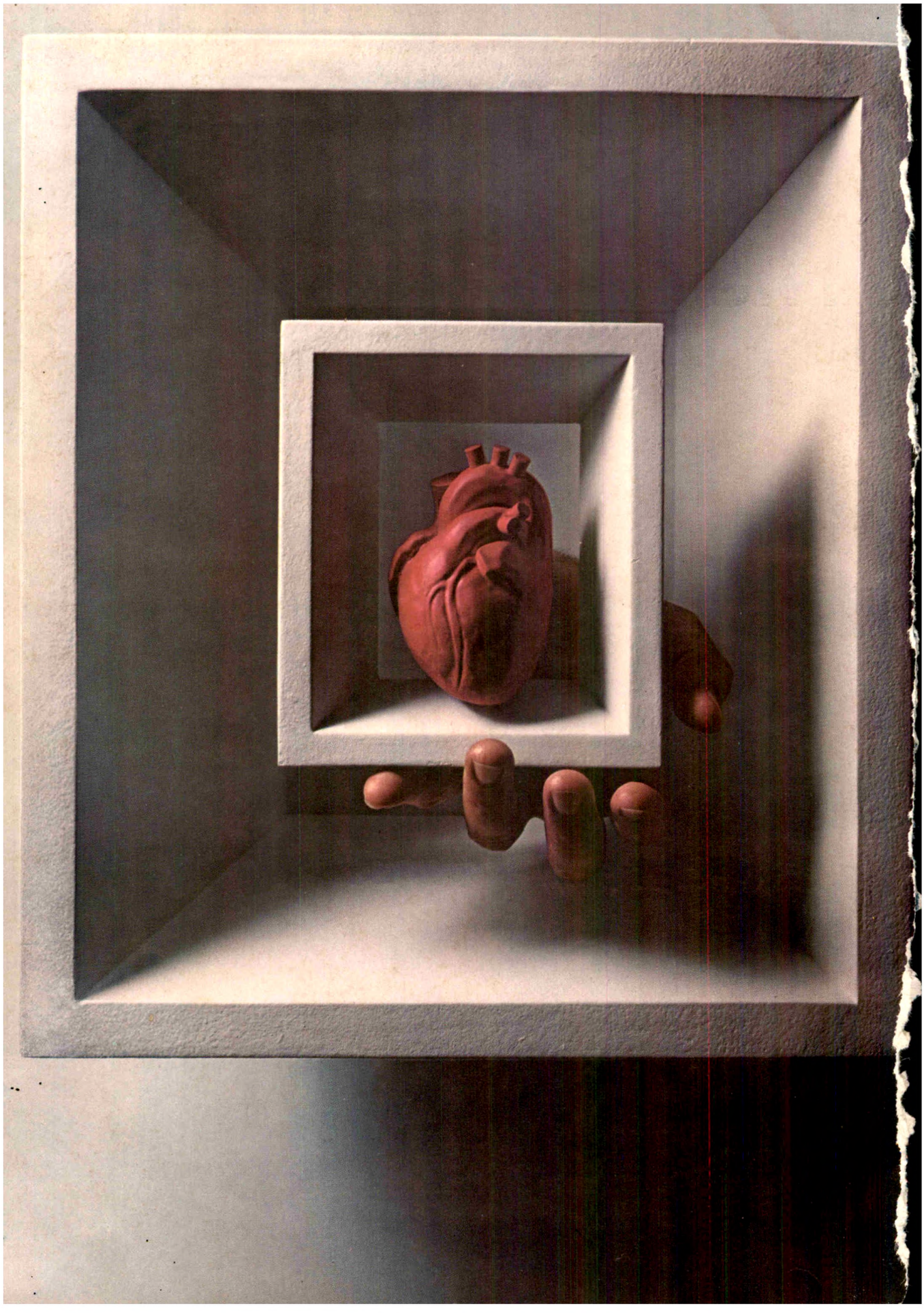

Angina Protection with Benefits for a Lifetime

ONCE-DAILY CONTROL WITH HEART-SAVING BENEFITS

By reducing heart rate and cardiac contractility, INDERAL LA helps protect the heart from the potentially serious and debilitating consequences of ischemia. A highly effective antianginal agent for around-the-clock control of symptoms, INDERAL LA also provides cardiovascular protection for a sense of security in the years ahead.

PROTECTION AND EXPERIENCE NO CALCIUM BLOCKER CAN MATCH

Unlike calcium blockers, INDERAL LA—either alone or with a nitrate—is recommended for early treatment of angina in the majority of patients. Equally important, INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use.

START WITH 80 MG ONCE DAILY

Dosage may be increased to 160 mg once daily, as needed, to achieve optimal control. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY **INDERAL® LA**
(PROPRANOLOL HCl) *LONG ACTING CAPSULES*

Ayerst

The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories

P24,138

JUST ONCE EACH DAY FOR SIMPLIFIED CORE THERAPY IN ANGINA

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the platelets of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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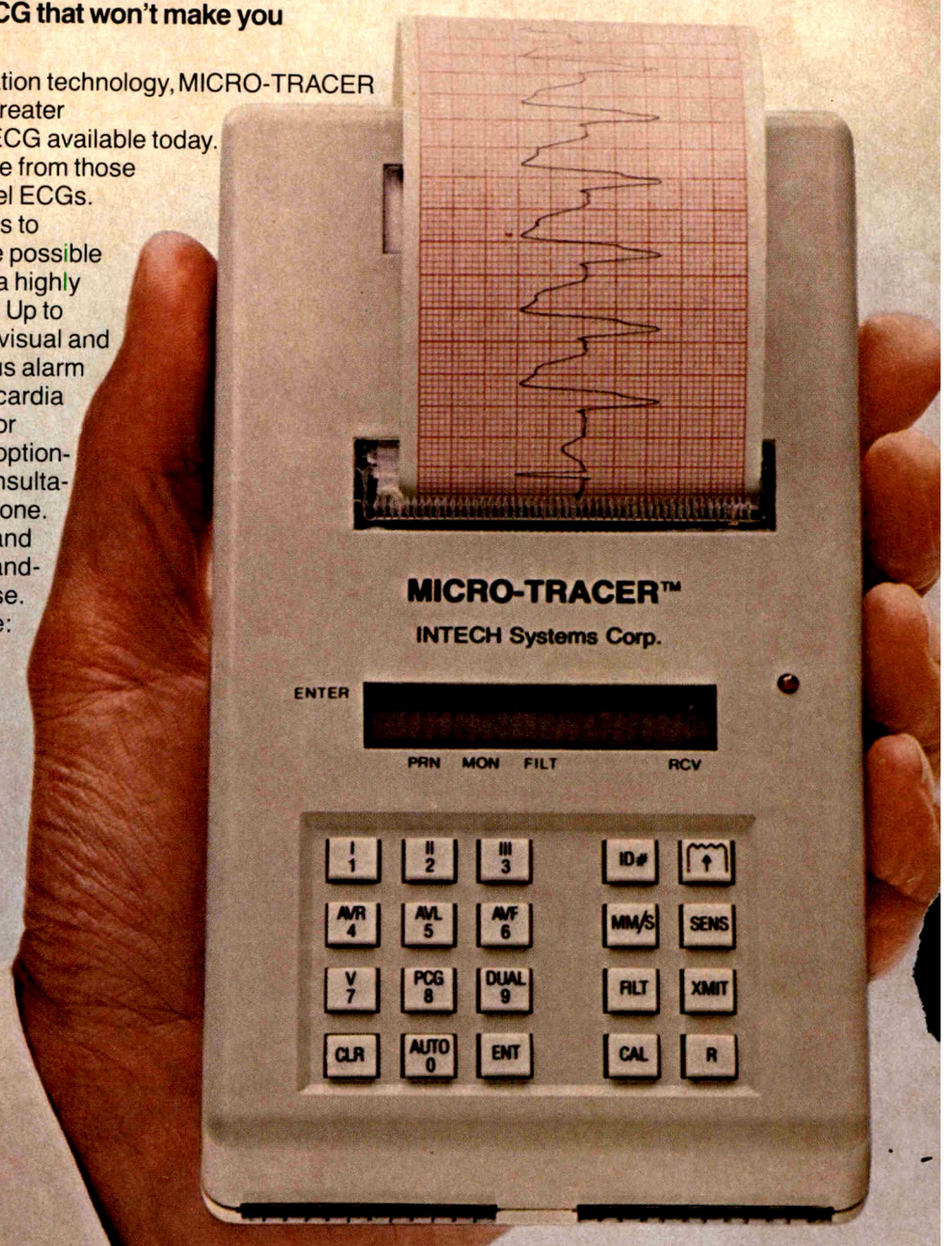

The Benefits of Less

Low doses of hydrochlorothiazide can provide most of the antihypertensive effect of larger doses.[1]

Increasing dosage above 25 mg. daily or improving bioavailability will not lead to increased antihypertensive efficacy in the majority of patients, but can result in a higher incidence of hypokalemia, hyperuricemia and hyperglycemia.[2]

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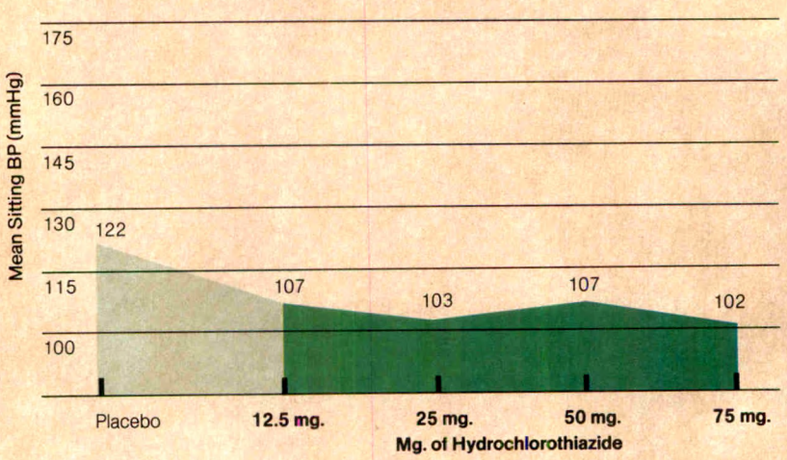

For the benefits of low dose diuretic therapy* with the added benefit of potassium-sparing triamterene

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DYAZIDE®

25 mg Hydrochlorothiazide/**50 mg** Triamterene/SKF

*Not for initial therapy. See boxed warning.

1. Kaplan, N.: Systemic Hypertension: Therapy, in Braunwald, E. (ed.), Heart Disease. A Textbook of Cardiovascular Medicine, Philadelphia, W.B. Saunders Co., vol. 1, pp. 922-951.
2. Dialogues in Hypertension, Hypertension Update II: New Developments in Antihypertensive Therapy, Jan. 1985, Health Learning Systems Inc.
3. Adapted from Beerman, B., and Groschinsky-Grind, M.: Antihypertensive Effect of Various Doses of Hydrochlorothiazide and Its Relation to the Plasma Level of the Drug, Eur. J. Clin. Pharmacol. 13: 195-201, 1978.

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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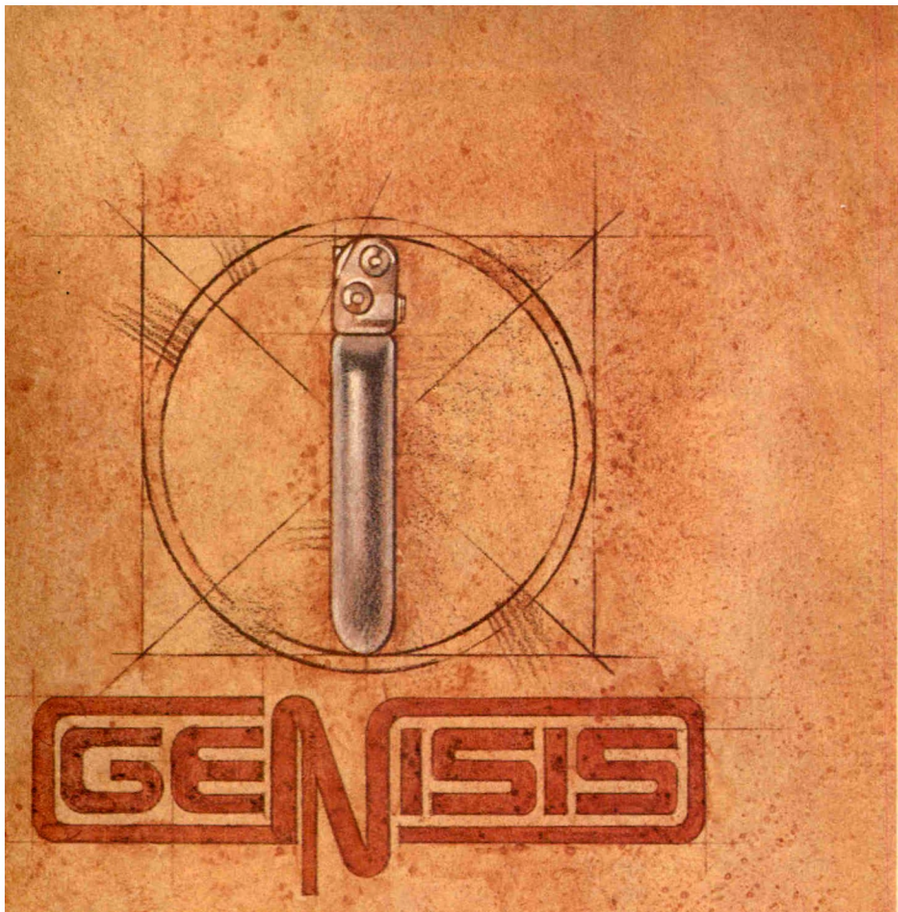

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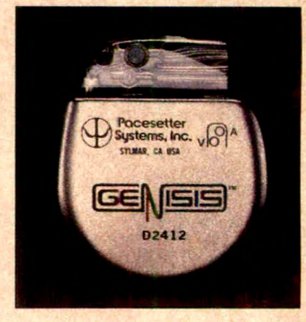

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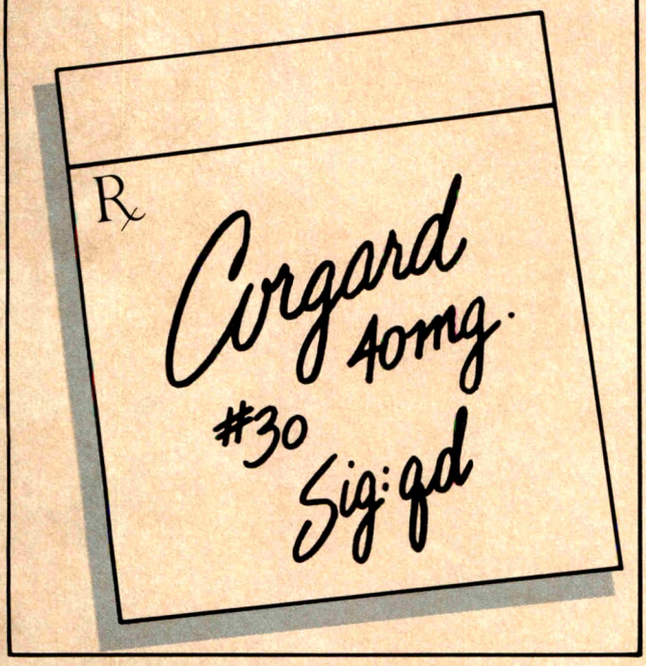
CORGARD®
(nadolol tablets)
R_x for Angina



CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy—In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia. The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a beta$_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

References: 1. Alexander JC, et al: Long-term experience with nadolol in the treatment of hypertension and angina pectoris. Am Heart J October Supplement 108 (4):1136-1140, 1984. 2. Data on file, Squibb Institute for Medical Research.

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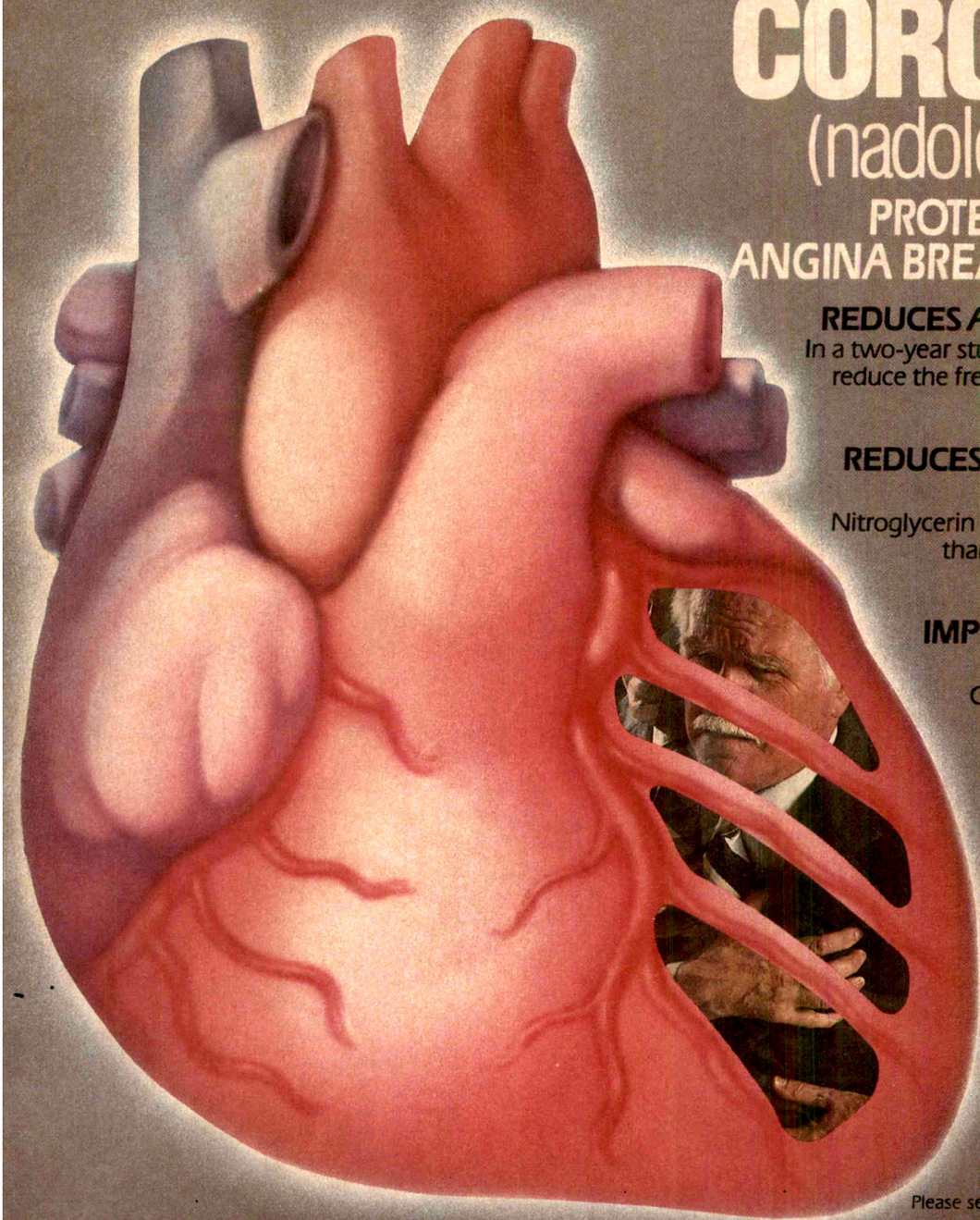

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*The syndrome of recurring symptoms compounded by the fear of impending attacks.

Please see brief summary of prescribing information on adjacent page.

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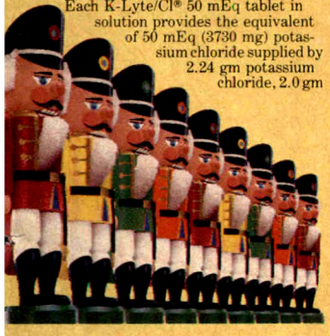

INDICATIONS AND USAGE: Therapy or prophylaxis of potassium deficiency.

CONTRAINDICATIONS: Contraindicated in patients with hyperkalemia. Hyperkalemia may complicate chronic renal impairment, metabolic acidosis, acute dehydration, and extensive tissue breakdown. Concomitant administration of potassium salts and potassium-sparing diuretic can produce severe hyperkalemia.

WARNINGS: In patients with impaired potassium excreting mechanisms, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and may be asymptomatic. Use in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. Acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of reduced total body potassium. Therefore, the treatment of potassium depletion requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the ECG, and the clinical status of the patient.

Information for Patients: Patients should be carefully directed to completely dissolve each tablet.

Drug Interactions: Simultaneous administration of potassium supplements and a potassium-sparing diuretic as well as concomitant use of potassium supplements and salt substitutes can result in hyperkalemia (see Contraindications).

Usage in Pregnancy - Pregnancy Category C: It is not known whether K-Lyte products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Nursing Mothers: There is a potential for serious adverse reactions in nursing infants from oral potassium supplements given to the mother. Nursing or the drug should be discontinued based on the importance of the drug for the mother.

Usage in Children: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: The most common adverse reactions to oral potassium supplements are nausea, vomiting, diarrhea and abdominal discomfort. These side effects occu more frequently when the medication is not taken with food or is not diluted properly or dissolved completely.

Hyperkalemia occurs only rarely in patients with normal renal function receiving potassium supplements orally.

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BRIEF SUMMARY

INDICATIONS—Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency of, or eliminate, anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack. Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.
PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.
ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.
DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25, 50 and 75 mg. For complete details, please see the full prescribing information.

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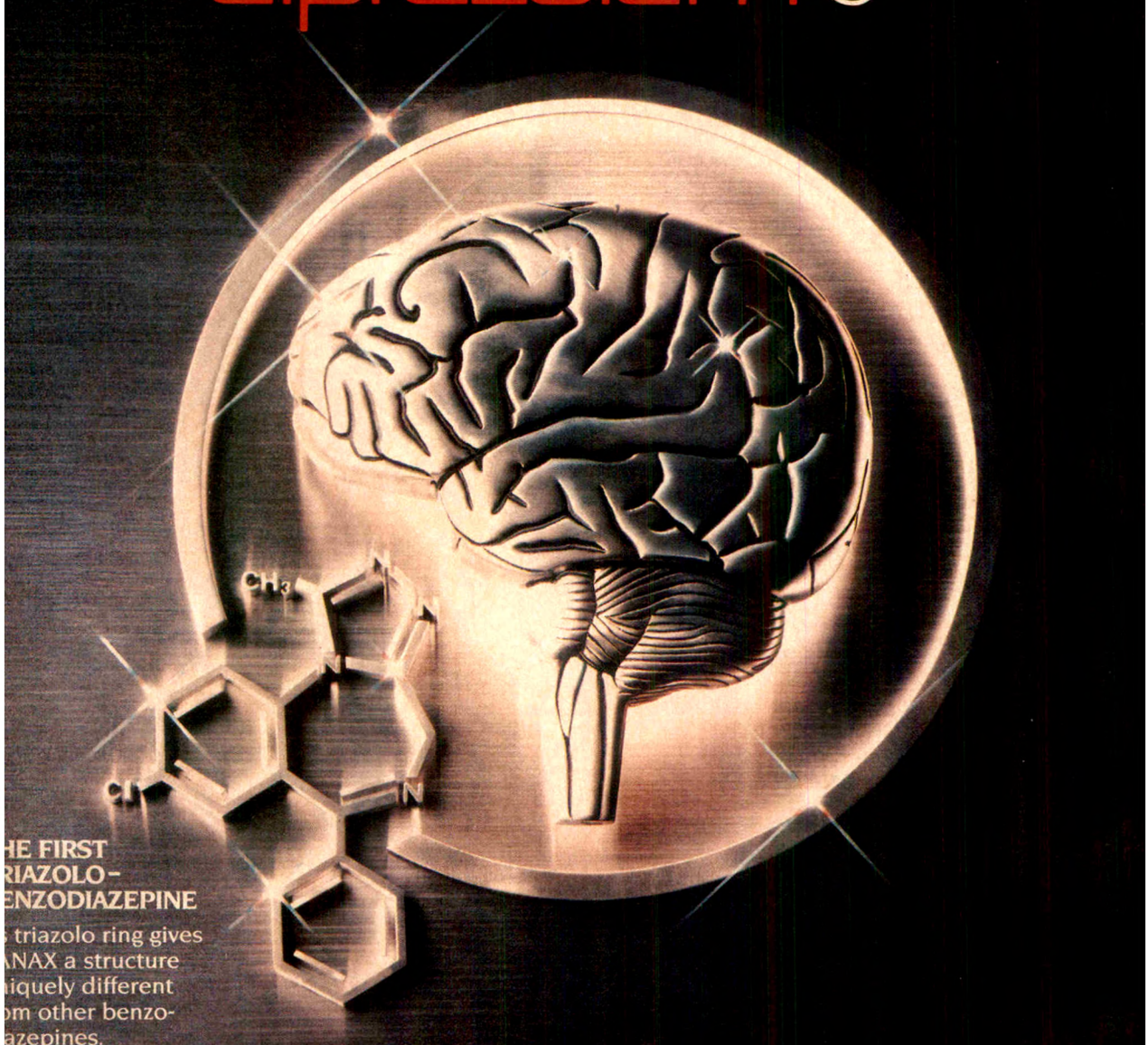

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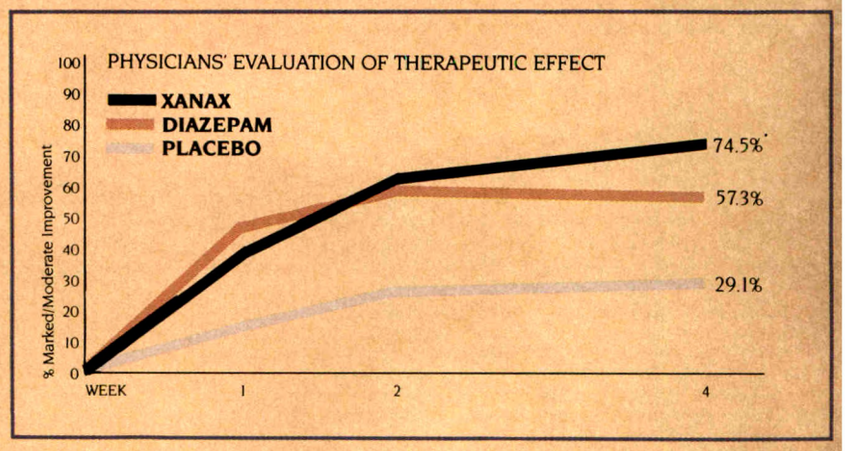
In double-blind, placebo-controlled clinical trials in 976 patients with moderate to severe clinical anxiety, therapy with XANAX was compared to diazepam:*

Patients treated with XANAX *had a significantly lower incidence of drowsiness when compared directly to diazepam* therapy in *a 976-patient*, placebo-controlled, multicenter study:*

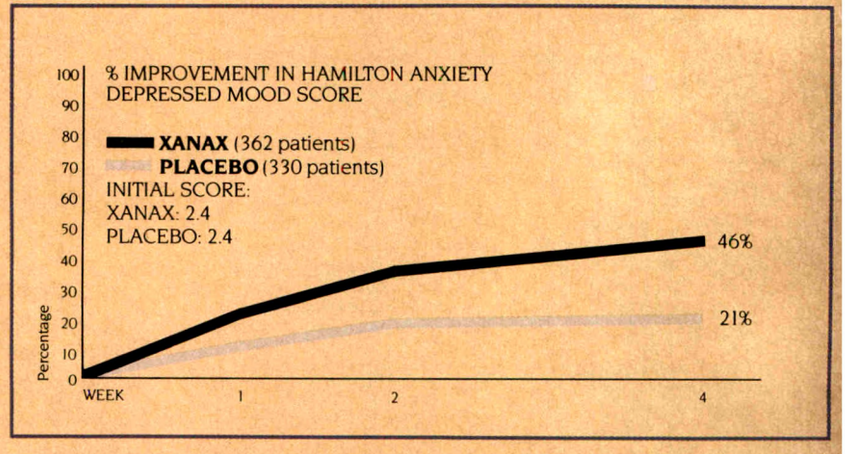


AND CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

EFFECTIVE IN CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

Patients with clinical anxiety may complain of having feelings of depression, such as sadness, blueness, or loneliness.

Depressed mood is one of 14 items on the Hamilton Anxiety Rating Scale. Special analysis of 692 anxious patients with a significant depressed mood item score showed that treatment with XANAX was significantly better than placebo in decreasing depressed mood score.



SIMPLE DOSAGE: XANAX 0.25–0.5 mg T.I.D.

The usual starting dose of XANAX is 0.25 to 0.5 mg, three times daily.

Please see next page for brief summary of prescribing information.

Xanax® 0.5 mg Tablets

alprazolam Ⓒ IV

alprazolam) Ⓒ

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-3-S

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. J Clin Psychiatry 42 (9):347-351, 1981.

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VOLUME 56

NUMBER 10

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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

571 **Simultaneous Computer Mapping to Facilitate Intraoperative Localization of Accessory Pathways in Patients with Wolff-Parkinson-White Syndrome**

JEFFREY B. KRAMER, PETER B. CORR, JAMES L. COX, FRANCIS X. WITKOWSKI, and MICHAEL E. CAIN

The clinical applicability of simultaneous intraoperative computer mapping from multiple sites was evaluated in 16 patients with the Wolff-Parkinson-White syndrome before surgical division of the accessory pathways. The computer mapping protocol permitted rapid, simultaneous recording and analysis of multiple epicardial and transmural electrograms along the atrioventricular groove. This approach facilitated intraoperative mapping by requiring only a single beat for analysis of anterograde and retrograde activation times, decreased cardiac manipulation during mapping, obviated the need for cardiopulmonary bypass, decreased the time required for mapping, permitted accurate study of nonsustained arrhythmias, and allowed rapid identification of multiple accessory pathways.

577 **Prospective Comparison of Holter Monitoring and Electrophysiologic Study in Patients with Coronary Artery Disease and Sustained Ventricular Tachyarrhythmias**

CHARLES D. SWERDLOW and JAN PETERSON

Baseline 24-hour Holter monitoring (HM) and electrophysiologic study (EPS) were compared in 32 consecutive patients with sustained ventricular tachyarrhythmias to determine the fraction of patients in which each could be performed and the fraction in which each could be used to guide therapy. Patients were excluded from HM if sustained ventricular tachycardia requiring termination occurred and from EPS if heart failure was sufficiently severe to cause excessive risk. More patients completed EPS than HM, but this difference was not significant (90% vs 71%, $p = 0.12$). Arrhythmias suitable for antiarrhythmic drug assessment were detected more frequently by EPS than HM: 87% vs 50% ($p = 0.003$) for all patients and 96% vs 70% ($p = 0.02$) for patients completing EPS or HM.

581 **Comparative Efficacy and Safety of Oral Tocainide and Quinidine for Benign and Potentially Lethal Ventricular Arrhythmias**

JOEL MORGANROTH, CARL OSHRAIN, and PETER P. STEELE

The antiarrhythmic efficacy and safety of tocainide and quinidine were compared in a double-blind, 3-center, parallel trial involving 133 patients with benign and potentially lethal ventricular arrhythmias (ventricular premature complexes [VPCs]). Baseline characteristics were not different between the 2 groups. Two weeks of placebo were followed by 8 weeks of active drug and then 2 weeks of placebo. Frequent Holter monitoring was used to judge efficacy. Ten of 27 patients (37%) receiving tocainide and 12 of 24 patients (50%) receiving quinidine had a 75% reduction in VPC frequency ($p > 0.25$). Total abolition of ventricular tachycardia occurred in 6 of 16 patients (37%) receiving tocainide and 6 of 13 patients (43%) receiving quinidine ($p > 0.25$). Conditions requiring discontinuation of therapy occurred in 18 of 67 patients (27%) receiving tocainide and 16 of 66 patients (24%) receiving quinidine (difference not significant). Quinidine caused a prolongation in the QT interval and tocainide caused a slight reduction. Thus, tocainide, the new oral analog of lidocaine, appears to be comparable to quinidine in safety and is slightly less effective in suppressing VPCs.

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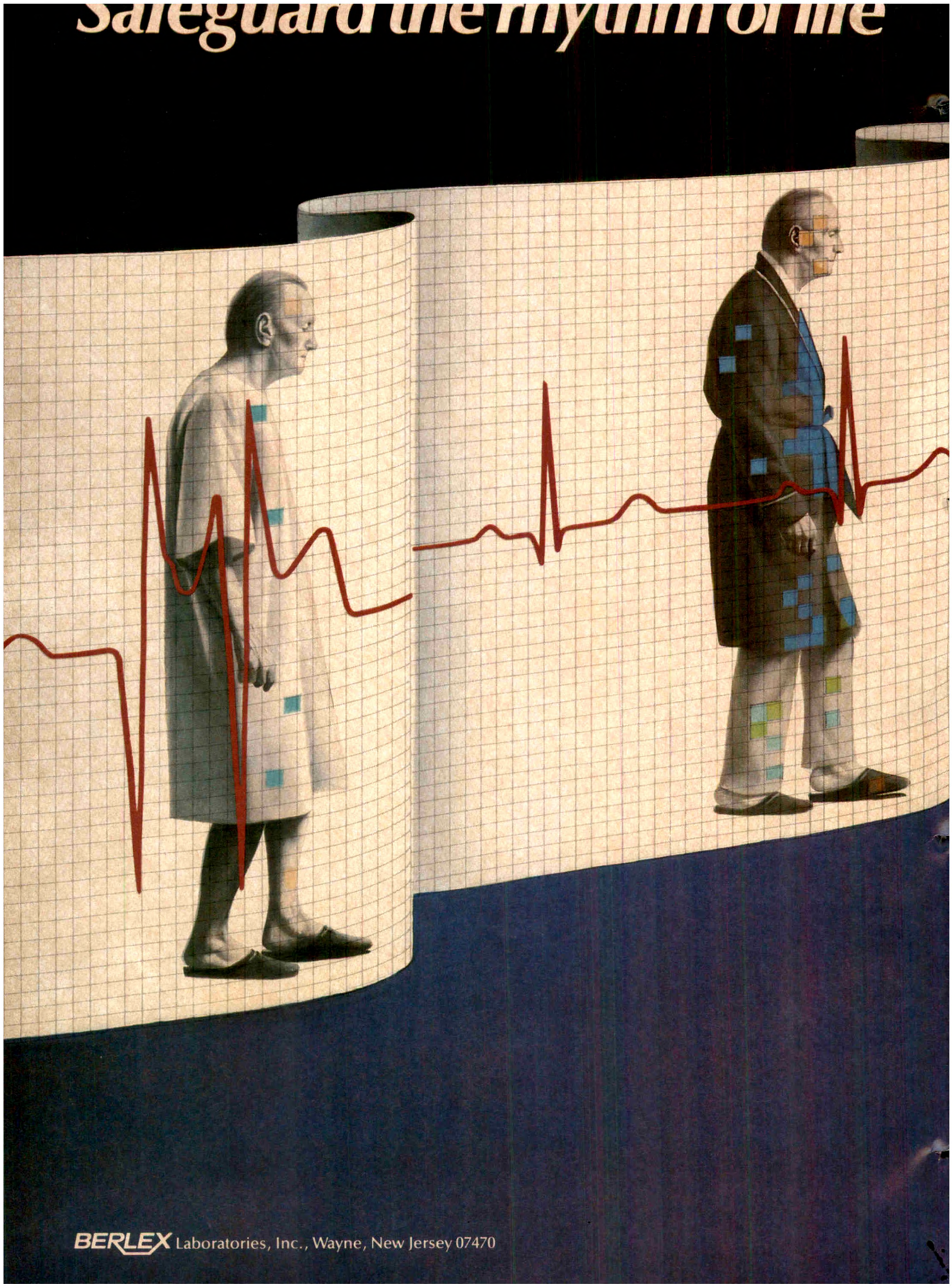
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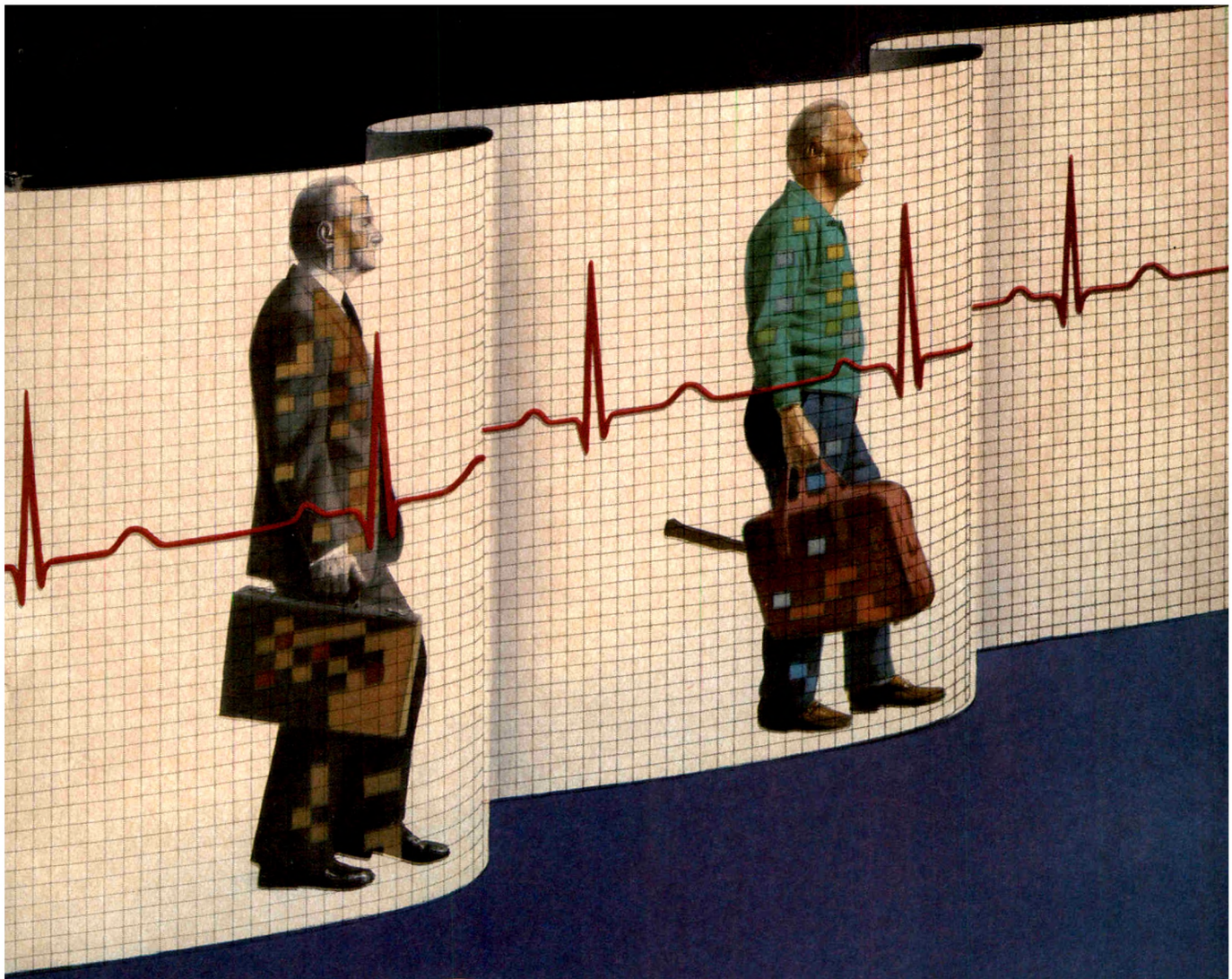

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References: 1. Selzer A: *Heart Lung* 1982;11:20-23.
2. Podrid P: *Patient Care* 1981;15:100-132.

Dura-Tabs are indicated in the prevention and/or treatment of:
1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock)
2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).
CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine. 2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered. 3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring. 4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals. 5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity. 7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal. 8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk. *Information for Patients:* As with all solid oral medications, Quinaglute (quinidine gluconate) Dura-Tabs (sustained-release tablets) should be taken with an adequate amount of fluid, preferably in an upright position, to facilitate swallowing.

Drug Interactions: *Drug*	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea. Less frequently encountered adverse reactions:
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope; disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.
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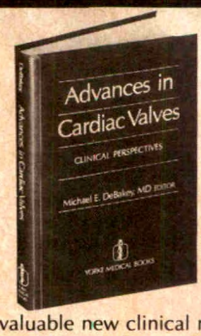

Advances in Cardiac Valves
Clinical Perspectives

edited by
Michael E. DeBakey, MD
0-914316-40-0, 1983, 274pp., $35.00

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585 **Incidence of Proarrhythmic Effects from Quinidine in the Outpatient Treatment of Benign or Potentially Lethal Ventricular Arrhythmias**

JOEL MORGANROTH and LEONARD N. HOROWITZ

The prevalence of proarrhythmic events secondary to the initiation of quinidine in outpatients with benign or potentially lethal ventricular arrhythmias was retrospectively reviewed in 360 patients treated with quinidine as part of 3 outpatient drug trials. These patients had at least 30 ventricular premature complexes (VPCs) per hour during placebo treatment and had no evidence of unstable clinical states, hypokalemia, digitalis toxicity, atrial fibrillation or a prolonged QT interval. Quinidine was dosed from 200 to 400 mg 4 times a day for 2 to 4 weeks and a proarrhythmic effect was defined by Holter monitoring. There was no difference in the demographic characteristics, response to quinidine therapy or side effects during quinidine treatment among the 3 trials. The proarrhythmic response rate was 6 of 360 (2%) and all patients were asymptomatic. Thus, quinidine can be safely initiated to outpatients as described above.

588 **Ambulatory Electrocardiographic Recordings at the Time of Fatal Cardiac Arrest**

PETER G. MILNER, EDWARD V. PLATIA, PHILIP R. REID, and LAWRENCE S.C. GRIFFITH

Ambulatory electrocardiographic recordings in 13 patients at the time of in-hospital cardiac arrest showed ventricular tachycardia (VT) to be the initial arrest arrhythmia in 12 patients. VT degenerated to ventricular fibrillation in 10 patients at a mean interval of 96 ± 31 seconds after cardiovascular collapse. A significant increase in VT runs occurred during the hour before arrest. Despite prompt resuscitation efforts, only 6 of 12 patients survived. Degeneration of VT to ventricular fibrillation within 30 seconds and a slower rate of VT at onset of arrest were associated with failure of resuscitation.

593 **Usefulness of Programmed Stimulation in Predicting Efficacy of Propafenone in Long-Term Antiarrhythmic Therapy for Paroxysmal Supraventricular Tachycardia**

MATTHIAS MANZ, GERHARD STEINBECK, and BERNDT LÜDERITZ

The electrophysiologic effects of intravenous and oral propafenone were evaluated in 24 patients with paroxysmal supraventricular tachycardia. Propafenone prolonged the effective refractory periods of the right atrium and the atrioventricular node. With propafenone, the cycle length of the reentrant tachycardia and the shortest atrial interval with 1:1 atrioventricular conduction increased markedly. The electrophysiologic effects of intravenous and oral propafenone were similar. Patients with complete suppression of supraventricular tachycardia appeared to have less recurrences during long-term therapy. Thus, acute electrophysiologic drug testing with propafenone can predict its efficacy during chronic therapy in most patients.

VALVULAR HEART DISEASE

598 **Effects of Atenolol on Exercise Capacity in Patients with Mitral Stenosis with Sinus Rhythm**

HERMAN O. KLEIN, PINHAS SARELI, COLON L. SCHAMROTH, YOONOOS CARIM, MENASHE EPSTEIN, and BRIDGET MARCUS

Exercise capacity is almost always impaired in patients with significant mitral stenosis and sinus rhythm, because elevation of left atrial pressure occurs with exercise-induced sinus tachycardia. Beta blockade with atenolol reduced mean heart rates at rest and during exercise in 13 patients with mitral stenosis in sinus rhythm ($p = 0.0015$) and significantly increased total exercise time ($p = 0.0015$) and maximal exercise capacity ($p = 0.0015$). Atenolol produces objective improvement of exercise capacity in patients with mitral stenosis in sinus rhythm. This is attributed to diminished effort-induced sinus tachycardia, thus improving left atrial emptying.

602 **Electrophysiologic Mechanisms of Provoked Atrial Flutter in Mitral Valve Prolapse Syndrome**

DAVID J. DOBMEYER, RONALD A. STINE, CARL V. LEIER, and STEPHEN F. SCHAAL

Patients with mitral valve prolapse (MVP) and sustained atrial flutter (AF) provoked by the extrastimulus technique in the catheterization laboratory were found to differ from patients without MVP with provokable AF by the absence of atrial conduction disease. The patients with MVP who had provokable AF had significant differences

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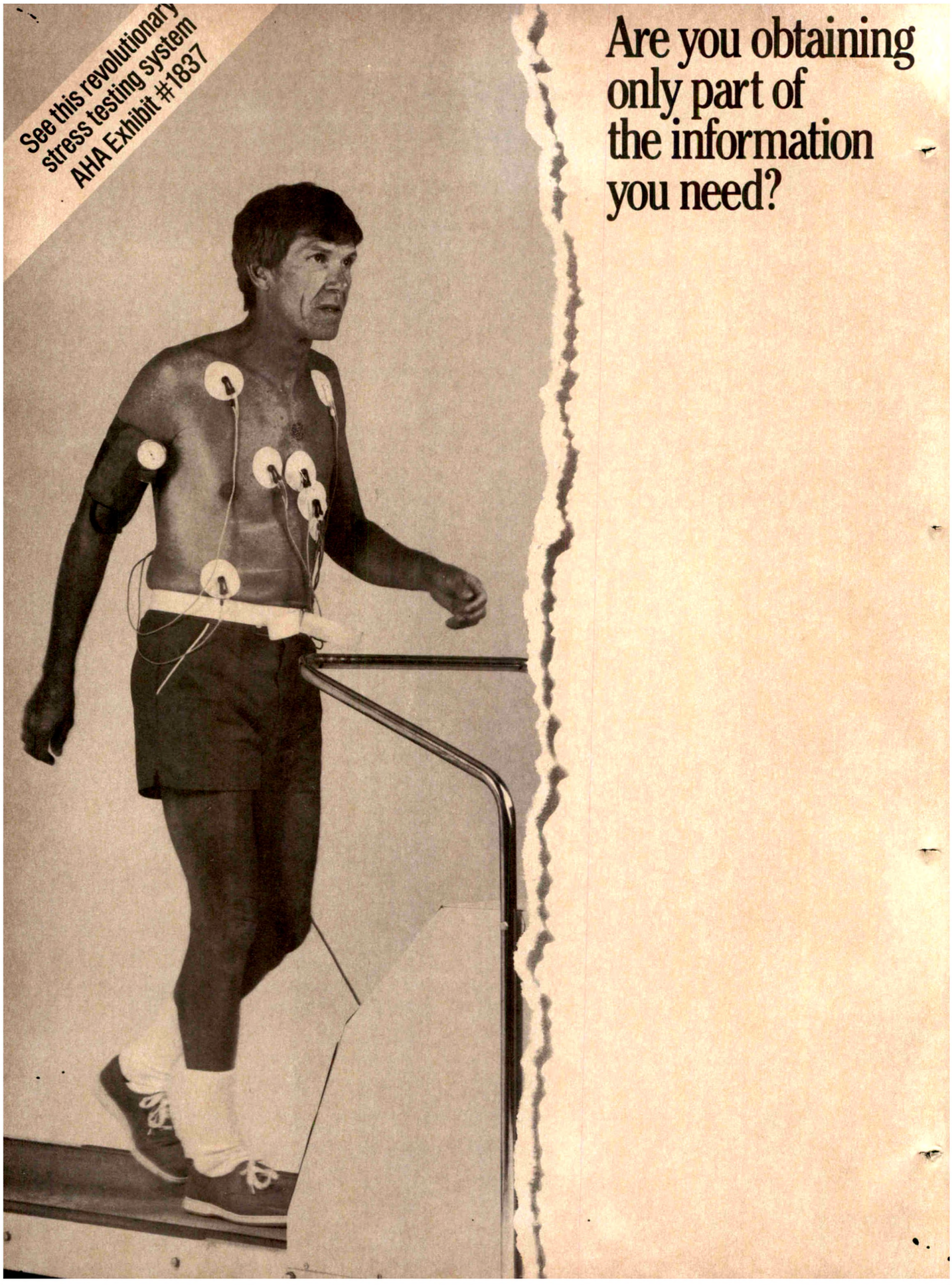

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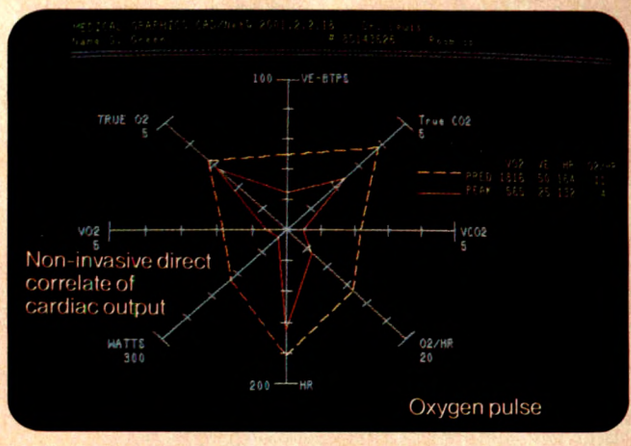

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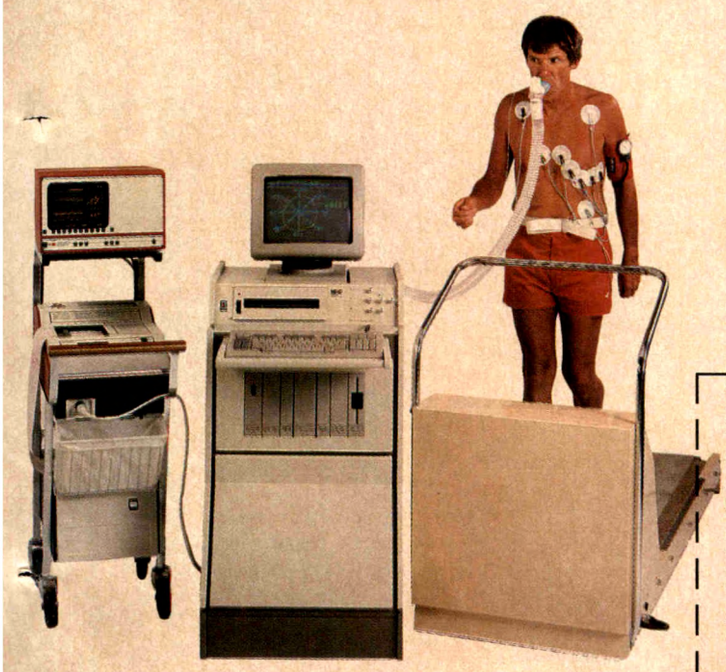

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between high and low right atrial effective refractory periods than did MVP patients without provokable AF and normal subjects. These findings suggest that inhomogeneities of refractory periods may cause AF in patients with MVP. This inhomogeneity may be a result of autonomic imbalance or abnormalities.

605 **Prognostic Significance of Exercise-Induced Left Ventricular Dysfunction in Chronic Aortic Regurgitation**
DAVID S. GEE, JACK E. JUNI, JOHN T. SANTINGA, and ANDREW J. BUDA

The significance of a preoperative decrease in exercise left ventricular (LV) ejection fraction (EF) in patients with chronic aortic regurgitation (AR) is uncertain. To examine this further, 23 patients were investigated who had hemodynamically significant AR and who underwent rest and exercise radionuclide angiography before and after valve replacement. Preoperatively, exercise LVEF decreased significantly ($p < 0.001$). Postoperatively, exercise LVEF increased significantly ($p < 0.01$ compared to preoperative values). After a mean follow-up of 30 months, most patients who survived surgery were asymptomatic and there were no late cardiac related deaths. Our data suggest that most patients improve exercise LVEF after valve replacement for chronic AR despite an abnormal preoperative exercise study. In addition, a preoperative decrease in exercise LVEF in patients with significant AR does not predict a poor postoperative outcome.

610 **Clinical and Echocardiographic Observations in Pulmonary Valve Endocarditis**
ANNE-CLAUDE CREMIEUX, SERGE WITCHITZ, MARIE-CHRISTINE MALERGUE, MICHEL WOLFF, DANIEL VITTECOCQ, JEAN-LOUIS VILDE, JACQUES FROTTIER, PIERRE ETIENNE VALERE, CLAUDE GIBERT, and ADRIEN G. SAIMOT

Clinical and echocardiographic data on 12 patients with pulmonary valve endocarditis are described. Seven patients had isolated pulmonary endocarditis and in 5 patients other valves were infected (aortic, tricuspid or mitral or all 3). Two patients were heroin addicts and 4 had underlying heart disease (congenital heart disease [3 patients] or aortic regurgitation [1 patient]). The organisms involved were alpha streptococci in 3 patients (all with underlying heart disease), *Staphylococcus aureus* in 4, *Streptococcus D bovis* in 1 patient and *Candida guillermondii* in 1. M-mode and 2-dimensional echocardiography, performed in 10 patients, revealed vegetations in 8. Pulsed Doppler echocardiography, performed in 6 patients, revealed pulmonary regurgitation in all 6. Four patients underwent surgery, 4 died, including 1 patient after heart surgery, and 5 recovered with antibiotic treatment.

CARDIOMYOPATHY

614 **Echocardiographic and Doppler Flow Observations in Obstructed and Nonobstructed Hypertrophic Cardiomyopathy**
JULIUS M. GARDIN, ALI DABESTANI, GORDON A. GLASGOW, SAMUEL BUTMAN, CORA S. BURN, and WALTER L. HENRY

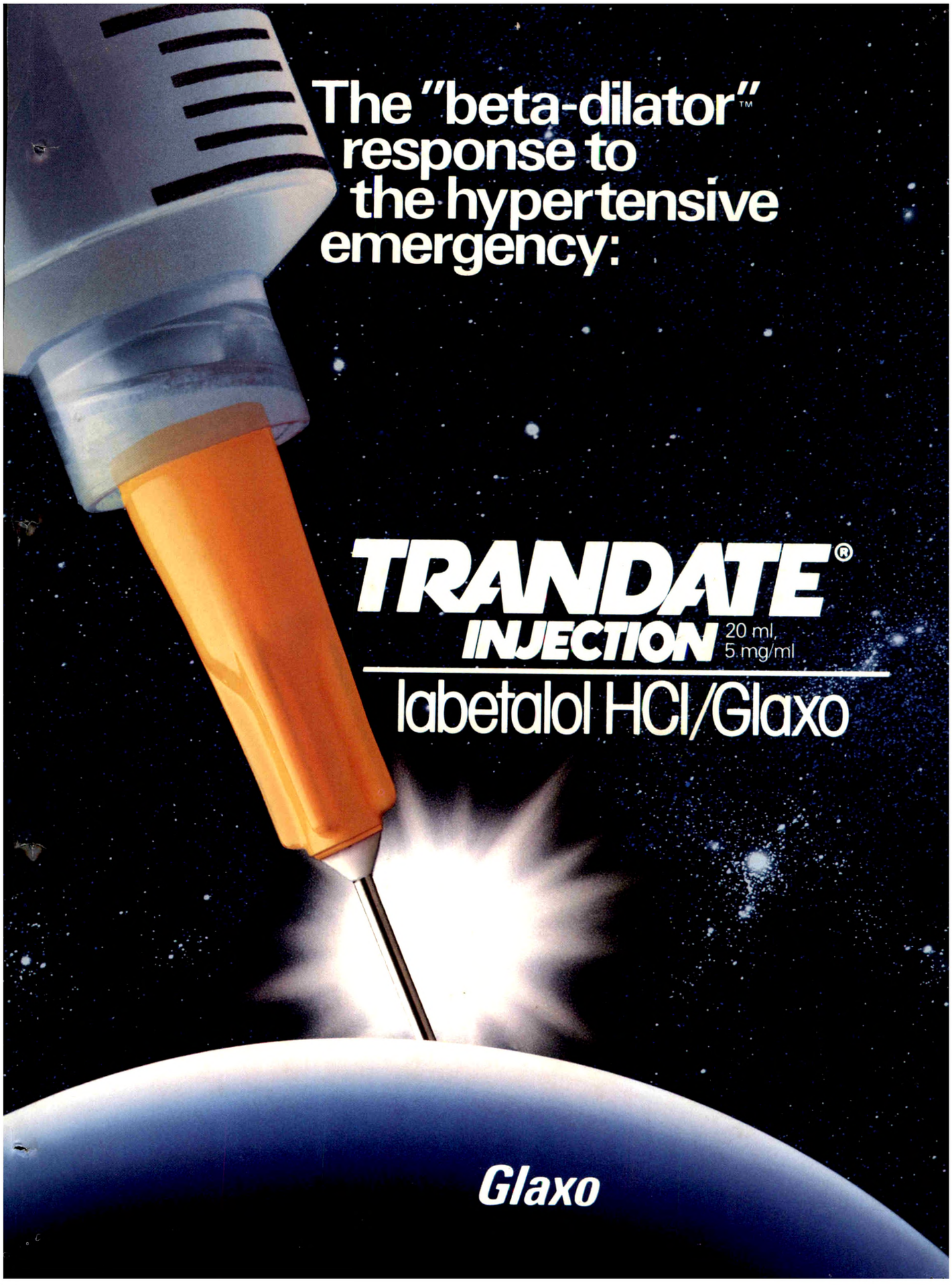
Doppler ascending aortic flow velocity was recorded in 20 patients with hypertrophic cardiomyopathy: 12 with left ventricular (LV) outflow gradients at rest (obstructed HC) and 8 without significant gradients (nonobstructed HC) and in 20 normal subjects. Peak aortic flow velocity was similar in all 3 groups. However, mean ejection time from the Doppler tracing or aortic valve echogram was significantly longer in patients with obstructed HC (345 ± 30 ms) than in those with nonobstructed HC (296 ± 24 ms, $p < 0.02$) or normal subjects (294 ± 19 ms, $p < 0.01$). A rapid midsystolic decrease in aortic flow velocity was seen in 11 of 12 patients with obstructed HC, but not in those with nonobstructed HC or normal subjects. Furthermore, Doppler left atrial recordings showed mitral regurgitation in 4 of 5 patients with obstructed HC but in none of 6 patients with nonobstructed HC. Continued LV minor-axis shortening and mitral regurgitant flow after mitral valve–septal contact suggests that early deceleration of aortic flow in the patient with obstructed HC is at least partially a result of impedance to LV outflow by the mitral valve with redirection of blood into the left atrium.

MISCELLANEOUS TOPICS

623 **Primary Acute Pericardial Disease: A Prospective Series of 231 Consecutive Patients**
G. PERMANYER-MIRALDA, J. SAGRISTÁ-SAULEDA, and J. SOLER-SOLER

A series of 231 patients with primary acute pericardial disease were studied according to a prospective protocol. In 32 patients (14%) a specific etiologic diagnosis was made. Diagnostic pericardiocentesis (32 patients) was performed when clinical activity and effusion persisted for longer than 1 week or when purulent pericarditis was

Continued on page A30


The "beta-dilator"™ response to the hypertensive emergency:
TRANDATE®
INJECTION 20 ml, 5 mg/ml
labetalol HCl/Glaxo
Glaxo

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80
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For hypertensive emergency

TRANDATE® INJECTION 20 ml, 5 mg/ml

labetalol HCl/Glaxo

The "beta-dilator™" response: control within minutes

Action within a minute. Trandate® (labetalol HCl/Glaxo) Injection rapidly, predictably lowers blood pressure by lowering total peripheral resistance (TPR), while maintaining cardiac output.[1,2] The "beta-dilator™" effect of simultaneous beta blockade and alpha blockade-induced vasodilation is apparent within a minute.

Rapid control. Full effect of an IV dose is apparent in 5 to 10 minutes: helps avoid hypotensive "overshoot," facilitates monitoring.

Cost control. Rapid effect may shorten hospital stay and beneficially affect costs under DRG's.

Well tolerated.* The most commonly reported adverse reactions: postural hypotension,† dizziness,† paresthesias, increased sweating and nausea.

Smooth transition to oral therapy with the same agent. Control of hypertensive crisis with Trandate Injection allows continued control on oral therapy with no need to change agents.

Trandate Injection—the "beta-dilator™" response to hypertensive emergencies...another original product of Glaxo research.

* Patients should always be kept in a supine position during IV drug administration. See **DOSAGE AND ADMINISTRATION** section of Prescribing Information before initiating therapy.

† The episodes of postural hypotension and dizziness occurred primarily in one study in which patients were placed in an upright position within three hours of dosing for evaluation.

For a discussion of **ADVERSE REACTIONS**, please see Brief Summary of Prescribing Information on the last page of this advertisement.

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For hypertensive emergency

TRANDATE® INJECTION 20 ml, 5 mg/ml

labetalol HCl/Glaxo

The "beta-dilator"™ response: control within minutes

- Trandate Injection can be administered as repeated IV injections, or by continuous infusion
- After initial dosing, further blood pressure reductions can be achieved with additional injections or by slow continuous infusion
- Discontinue Trandate Injection when blood pressure goal is achieved—when supine blood pressure has begun to rise, oral therapy may be initiated
- Patients should be kept in the supine position during IV drug administration. See **DOSAGE AND ADMINISTRATION** section of Prescribing Information before initiating therapy

For a discussion of **ADVERSE REACTIONS**, please see Brief Summary of Prescribing Information on the last page of this advertisement.

References: 1. Wallin JD, O'Neill WM Jr: Labetalol, current research and therapeutic status. *Arch Intern Med* 1983; 143:485-490. **2.** MacCarthy EP, Bloomfield S: Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. *Pharmacotherapy* 1983;3(4):193-219.

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TRN 138

Printed in U.S.A.

March 1985

TRANDATE® Injection
(labetalol hydrochloride)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: TRANDATE® (labetalol HCl) Injection is indicated for control of blood pressure in severe hypertension.

CONTRAINDICATIONS: TRANDATE® Injection is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitilization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Ischemic Heart Disease: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TRANDATE is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.

Nonallergic Bronchospasm (eg, chronic bronchitis and emphysema): Since TRANDATE Injection at the usual intravenous therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.

Pheochromocytoma: Intravenous labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

Rapid Decreases of Blood Pressure: Caution must be observed when reducing severely elevated blood pressure. Although such findings have not been reported with intravenous labetalol HCl, a number of adverse reactions, including cerebral infarction, optic nerve infarction, angina and ischemic changes in the electrocardiogram, have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as 1 or 2 days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

PRECAUTIONS: General: ***Impaired hepatic function*** may diminish metabolism of TRANDATE® Injection.

Hypotension: Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

Jaundice or Hepatic Dysfunction: On rare occasions, oral labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) TRANDATE Injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.

When the patient is started on TRANDATE Tablets, following adequate control of blood pressure with TRANDATE Injection, appropriate directions for titration of dosage should be provided (see **DOSAGE AND ADMINISTRATION**).

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted: While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: Routine laboratory tests are ordinarily not required before or after intravenous labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: Since TRANDATE (labetalol HCl) Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C: Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the MRHD, respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE® (labetalol HCl) Injection is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: TRANDATE® Injection is usually well tolerated. Most adverse effects have been mild and transient and, in controlled trials involving 92 patients, did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with TRANDATE Injection with the incidence per 100 patients as noted:

Cardiovascular System: Ventricular arrhythmia in 1.

Central and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/skin in 7; hypoesthesia (numbness) and vertigo in 1 each.

Gastrointestinal System: Nausea in 13; vomiting in 4; dyspepsia and taste distortion in 1 each.

Metabolic Disorders: Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.

Psychiatric Disorders: Somnolence/yawning in 3.

Respiratory System: Wheezing in 1.

Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see TRANDATE Tablet Product Information for details.) Certain of the side effects increased with increasing oral dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are probably or possibly dose-related.

Labetalol HCl Daily Dose (mg)	**200**	**300**	**400**	**600**	**800**	**900**	**1200**	**1600**	**2400**
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	2	3	3	3	5	1	9	13	16
Fatigue	2	1	4	4	5	3	7	6	10
Nausea	<1	0	1	2	4	0	7	11	19
Vomiting	0	0	<1	<1	<1	0	1	2	3
Dyspepsia	1	0	2	1	1	0	2	2	4
Paresthesias	2	0	2	2	1	1	2	5	5
Nasal Stuffiness	1	1	2	2	2	2	4	5	6
Ejaculation Failure	0	2	1	2	3	0	4	3	5
Impotence	1	1	1	1	2	4	3	4	3
Edema	1	0	1	1	1	0	1	2	2

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl during investigational use and extensive foreign marketing experience.

Clinical Laboratory Tests: Among patients dosed with TRANDATE Tablets, there have been reversible increases of serum transaminases in 4% of patients tested and, more rarely, reversible increases in blood urea.

OVERDOSAGE: Overdosage with TRANDATE® Injection causes excessive hypotension which is posture sensitive and, sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: **Excessive bradycardia**—administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac failure**—administer a digitalis glycoside and a diuretic. **Hypotension**—administer vasopressors, eg, norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. **Bronchospasm**—administer a beta$_2$-stimulating agent and/or a theophylline preparation.

If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION: Initiation of Dosing with TRANDATE Tablets: Subsequent oral dosing with TRANDATE Tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 mg or 400 mg, depending on the blood pressure response. Thereafter, **inpatient titration with TRANDATE Tablets may proceed as follows:**

Inpatient Titration Instructions

Regimen	Daily Dose*
200 mg bid	400 mg
400 mg bid	800 mg
800 mg bid	1600 mg
1200 mg bid	2400 mg

*If needed, the total daily dose may be given in three divided doses.

While in the hospital, the dosage of TRANDATE (labetalol HCl) Tablets may be increased at one-day intervals to achieve the desired blood pressure reduction.

For subsequent outpatient titration or maintenance dosing see TRANDATE Tablets Product Information **DOSAGE AND ADMINISTRATION** for additional recommendations.

HOW SUPPLIED: TRANDATE® Injection, 5 mg/ml, is supplied in 20 ml (100 mg) ampules, box of 1 (NDC 0173-0350-59).

Store between 2° and 30° C (36° and 86° F.) Do not freeze.

Manufactured for Glaxo Inc. Research Triangle Park, NC 27709 by Schering Pharmaceutical Corporation (PR), Manati, PR 00701

October 1984

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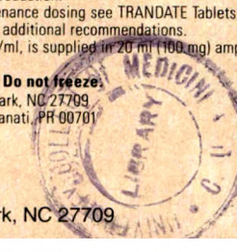

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suspected; therapeutic pericardiocentesis (44 patients) was performed to treat tamponade. Diagnostic biopsy (20 patients) was carried out when illness persisted for longer than 3 weeks; therapeutic biopsy was performed whenever pericardiocentesis failed to relieve tamponade. The diagnostic yield difference between diagnostic (6%) and therapeutic (35%) procedures was significant ($p < 0.001$). Thus, a diagnostic procedure is not warranted as a routine method. A choice between therapeutic pericardiocentesis and biopsy is circumstantial and has to be individualized. Only through a systematic approach can a substantial diagnostic yield be reached in primary acute pericardial disease.

631 Post-Cardiac Injury Syndrome and an Increased Humoral Immune Response Against the Major Contractile Proteins (Actin and Myosin)

IVAN DE SCHEERDER, JOEL VANDEKERCKHOVE, JOHAN ROBBRECHT, LUC ALGOED, MARC DE BUYZERE, JORIS DE LANGHE, GUIDO DE SCHRIJVER, and DENIS CLEMENT

Two models of cardiac injury were studied—cardiotomy (CT) and acute myocardial infarction (AMI)—and the level of anti-heart antibodies was determined. Significantly more patients had post–cardiac injury syndrome (PCIS) after CT than after AMI. CT patients showed a significantly higher humoral immune response than the AMI patients.

634 Cardiovascular Deconditioning Produced by 20 Hours of Bedrest with Head-Down Tilt (−5°) in Middle-Aged Healthy Men

F. ANDREW GAFFNEY, J.V. NIXON, ERLING S. KARLSSON, WILLIAM CAMPBELL, A.B.C. DOWDEY, and C. GUNNAR BLOMQVIST

Cardiovascular deconditioning after prolonged bedrest has been attributed mainly to inactivity. To examine the role of body fluid shifts, 5 healthy middle-aged men were studied before, during and after a 20-hour period of bedrest with head-down tilt (−5°). This intervention produces a marked central shift of intravascular and interstitial fluid, but the short duration minimizes effects of inactivity. Central venous pressure, cardiac output and stroke volume increased initially but returned to baseline levels within 20 hours. Supine central venous pressure after tilt was lower than the value before tilt. After tilt there was orthostatic intolerance and a decreased maximal oxygen consumption associated with higher heart rates, lower stroke volumes and a 0.51-liter decrease in blood volume. These hemodynamic conditions were qualitatively and quantitatively similar to those seen after 2 to 3 weeks of bedrest or spaceflight. The results support the concept that cardiovascular deconditioning after bedrest is primarily an adaptation to a postural fluid shift rather than to inactivity.

639 Safety of Outpatient Cardiac Catheterizations

W. PETER KLINKE, GEORGE KUBAC, TAL TALIBI, and SIMON J.K. LEE

All outpatient cardiac catheterizations performed over a 66-month period were analyzed. A total of 3,071 outpatient cardiac catheterizations (83% of all catheterizations) were performed. The Judkins approach was used in over 98% of the catheterizations and 79% of the patients had both right- and left-sided cardiac catheterizations and coronary angiography. More than 86% of patients had significant coronary, valvular, myocardial or congenital heart disease. Thirty-four patients (1.1%) had a major complication, including 4 deaths (0.13%). Seventy patients (2.3%) were admitted for observation and discharged the following day with no major complications. More than 96% of all patients were discharged the same day. These results are similar to those of previous studies of cardiac catheterization. It is concluded that outpatient cardiac catheterization is safe and efficient.

642 Relation of Hemoglobin A_1 and Blood Glucose to Cardiac Function in Diabetes Mellitus

RICHARD S. GOLDWEIT, JEFFREY S. BORER, LOIS G. JOVANOVIC, ANDREW J. DREXLER, CLARE A. HOCHREITER, RICHARD B. DEVEREUX, and CHARLES M. PETERSON

The relation of short- and long-term changes in glucose metabolism to cardiac function was studied in 10 young insulin-dependent diabetic patients without clinical evidence of heart disease. Radionuclide cineangiography and echocardiography were used before and after both acute variations in blood glucose levels, and induction of chronic "tight glucose control" involving normalization of hemoglobin A_1. In diabetic patients, left ventricular (LV) ejection fraction (EF) at normal blood glucose concentration was indistinguishable from values in 11 normal

Continued on page A36

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ENDOWED CHAIR IN CARDIOVASCULAR RESEARCH:
The Department of Medicine of the University of Florida, College of Medicine is seeking applications for an endowed Chair in Cardiovascular Research. The endowed Chair, with assets in excess of one million dollars, was established by the State of Florida's Eminent Scholars Program and was made possible by generous contributions from the Suncoast Heart Association. The individual who will fill the Chair will have a full-time faculty appointment (Professor) in the Division of Cardiology of the Department of Medicine of the University of Florida College of Medicine. The appointee should have an M.D. or Ph.D. degree and a well-established, creative and productive investigative program in cardiovascular research. Salary is negotiable. Anticipated starting date is July 1, 1986. Interested individuals should write by February 28, 1986: James E. McGuigan, M.D., Chairman, Search Committee, Chair in Cardiovascular Research, Department of Medicine, College of Medicine, Box J-277, University of Florida Health Center, Gainesville, FL 32610. The University of Florida is an Equal Opportunity/Affirmative Action Employer.

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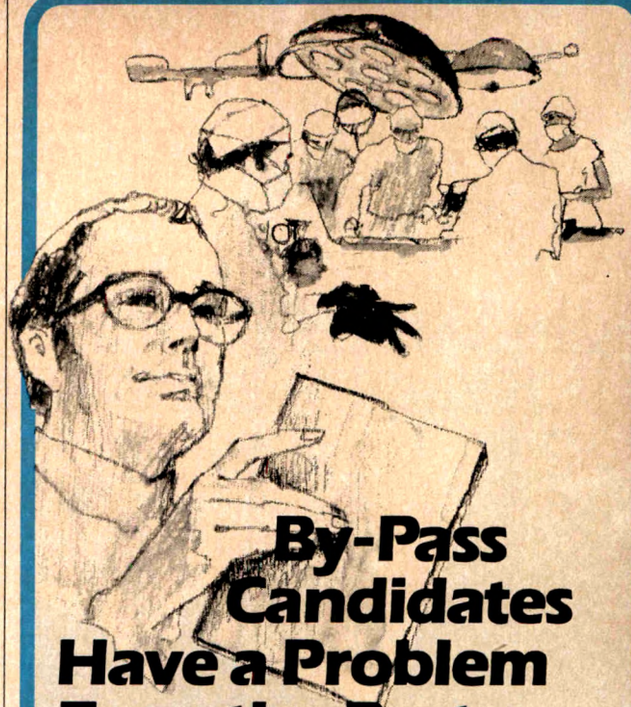
Full-Time Faculty position at Assistant Professor level available January 1, 1986 in the Division of Cardiology, University of Colorado Health Sciences Center. Applicants must be fully trained in Cardiology with special emphasis on cardiac catheterization. Applicants should have extensive training and be desirous of growth in independent cardiovascular research; preference will be given to those with a dedicated interest in basic cardiovascular research. DEADLINE FOR APPLICATIONS is November 15, 1985. Send curriculum vitae to: L. D. Horwitz, M.D., Head, Division of Cardiology, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, Box B-130, Denver, CO 80262. The University of Colorado Health Sciences Center is an equal Opportunity Employer.



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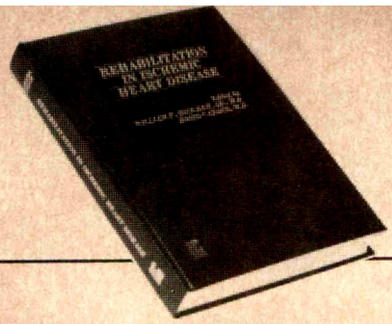

REHABILITATION IN ISCHEMIC HEART DISEASE

Edited by **William P. Blocker, Jr., M.D.,** F.A.C.P., Chief, Rehabilitation Medicine Service, V.A. Hospital, Houston, Assistant Professor of Physical Medicine, Baylor College of Medicine, Houston, and **David Cardus,** M.D., F.A.C.C., Professor of Physiology and Rehabilitation, Baylor College of Medicine, Houston, Texas.

Heavily illustrated, this volume presents 60 self-contained chapters dealing with *all* aspects of rehabilitation of the patient with ischemic heart disease. The 45 noted contributors discuss topics such as: designing a cardiac rehabilitation center; methods of rehabilitation for the stroke patient, amputee, spinal cord injury patient who has had a heart attack; equipment needs for a cardiac rehabilitation center; and legal responsibilities of the physicians and therapists.

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500 pp., 188 figs. & tbls., large format 8½ × 11, 1982, $80.00

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Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

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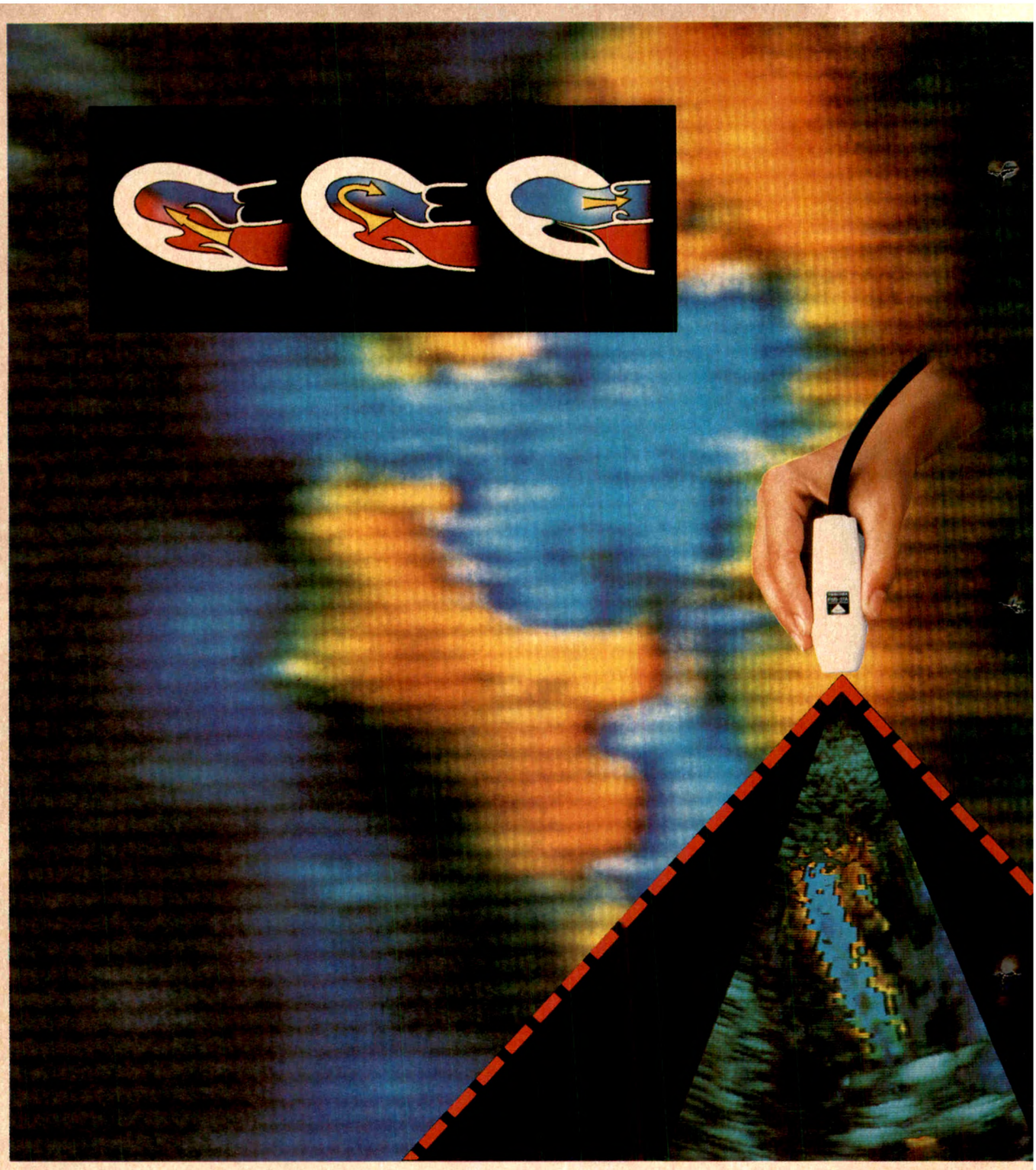

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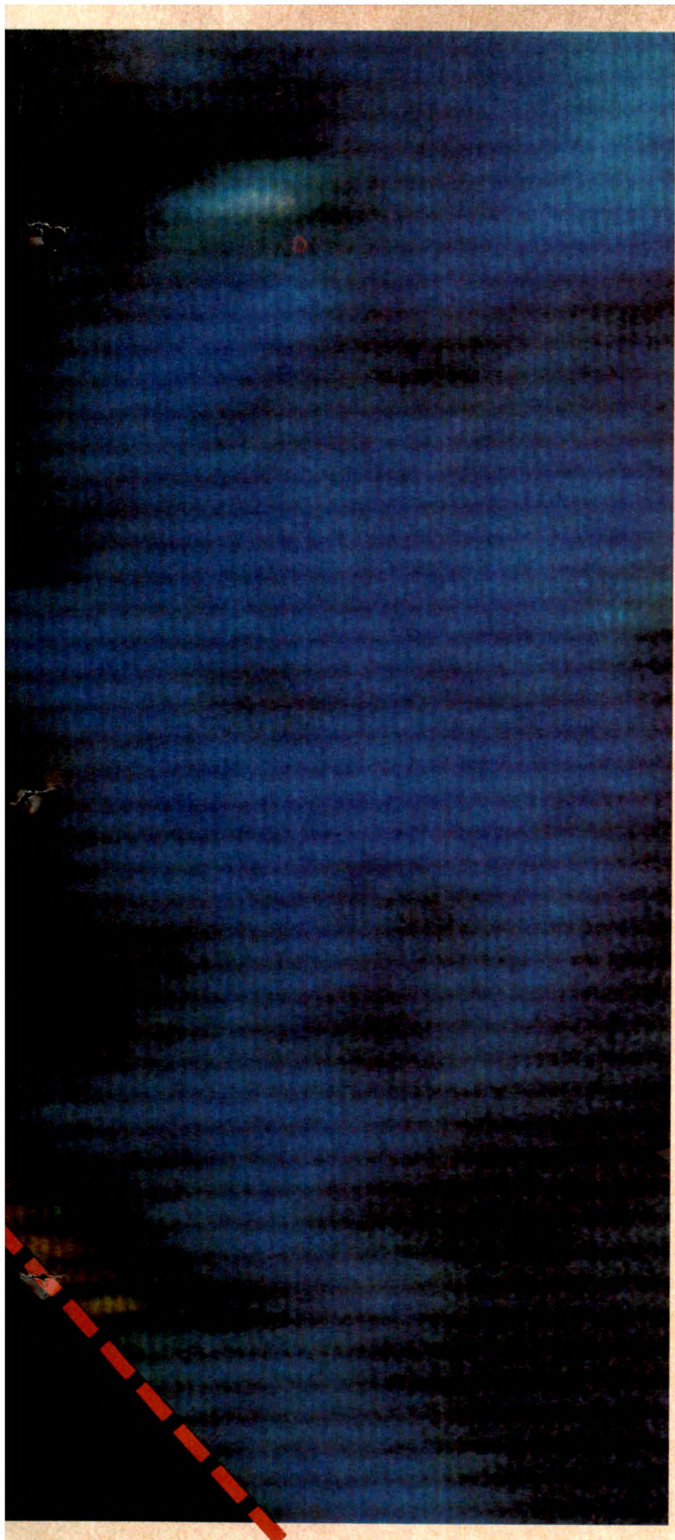

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subjects. However, during hyperglycemia (about 300 mg/dl), average EF at rest was 61%, significantly higher than during normoglycemia (56%). No significant change in LV diastolic dimension was noted in association with shifts in glucose concentrations. Normalization of hemoglobin A_1 was achieved in 6 to 25 weeks, and had no significant effect on LVEF or response of systolic function to blood glucose levels. Thus, in insulin-dependent diabetic patients with overt heart disease, variation in blood glucose, but not hemoglobin A_1, is associated with small but significant changes in systolic function.

647 Electrophysiologic Evaluation of the Cardiac Conduction System and Its Autonomic Regulation in Familial Amyloid Polyneuropathy

BO LENNART BERGFELDT, BERT-OVE OLOFSSON, and KNUT OLOF EDHAG

Cardiac conduction disturbances are a salient feature in familial amyloid polyneuropathy (FAP), and amyloid infiltration of the conduction system has been found. This study is the first to have been undertaken to evaluate the function of the cardiac conduction system and its autonomic regulation during an invasive electrophysiologic study. Seven patients with FAP and with severe disturbances of the conduction system were studied and in 3 of them the parasympathetic regulation was found to be abolished. In 1 patient the observations indicated either vagal overactivity or denervation oversensitivity of the receptors. The function of β adrenoceptors was intact in all patients. Thus, dysfunction of the autonomic nervous regulation of the cardiac conduction system was found in 4 of 7 patients. Autonomic neuropathy of the heart in FAP has been demonstrated. However, most conduction abnormalities were irreversible, indicating amyloid infiltration of the conduction system as the predominant pathophysiologic mechanism.

653 Atrial Septal Aneurysm: Echopolycardiographic Study

CARLO LONGHINI, MARIA CHRISTIANA BRUNAZZI, GIANFRANCA MUSACCI, MARZIA CANEVA, ATTILIO BANDELLO, LORENZO BOLOMINI, MARIO BARBIERO, TIZIANO TOSELLI, and FRANCO BARBARESI

Atrial septal aneurysm with diagnosis during life is a rare reported anomaly. Among 4,000 routine echocardiograms, 23 cases of atrial septal aneurysm were found. Echocardiography revealed various motion patterns of atrial septal aneurysm. No phonomechanocardiographic findings were related to the presence of the atrial septal aneurysm. This study shows a greater incidence of aneurysm of the atrial septum in living patients than has been reported previously, and because of the potential risk, suggests the necessity for a systematic research of the atrial septal aneurysm during each routine echocardiographic examination, even if no specific clinical or phonocardiographic findings are present.

EXPERIMENTAL STUDIES

657 Measurement of Cardiac Output by Cine Computed Tomography

JEFFREY S. GARRETT, PETER LANZER, WERNER JASCHKE, ELIAS BOTVINICK, RICHARD SIEVERS, CHARLES B. HIGGINS, and MARTIN J. LIPTON

High-speed computed transmission tomography (cine CT) is a new noninvasive technique that is useful for the rapid, accurate quantitation of cardiac function. The capability of cine CT to assess cardiac output was examined in 10 mongrel dogs as an initial step in validating this method. Scans and thermodilution measurements of cardiac output were obtained at rest and during altered hemodynamic states induced by separate infusions of dobutamine and phenylephrine. Using the Stewart-Hamilton equation established for indicator dilution techniques, cardiac output was calculated. The results established a direct linear correlation ($r = 0.92$) between cine CT cardiac output and thermodilution cardiac output over a wide range of cardiac outputs (1.5 to 6.3 liters/min). This study demonstrates that cine CT can provide a reliable estimate of cardiac output noninvasively using contrast medium as an indicator in dogs.

662 Reduction of Laser-Induced Pathologic Tissue Injury Using Pulsed Energy Delivery

LAWRENCE I. DECKELBAUM, JEFFREY M. ISNER, ROBERTA FORTIN DONALDSON, RICHARD H. CLARKE, SYLVIE LALIBERTE, ALON S. AHARON, and JEFFREY S. BERNSTEIN

To determine if the pathologic injury typical of continuous-wave laser irradiation can be eliminated by altering the profile of laser energy delivery, 145 myocardial slices were irradiated using wavelengths of 248, 355, 488 to 515, 532, 1,064 or 10,600 nm from either an excimer, Nd-YAG, argon or CO_2 laser. Energy profile ranged from

Continued on page A42

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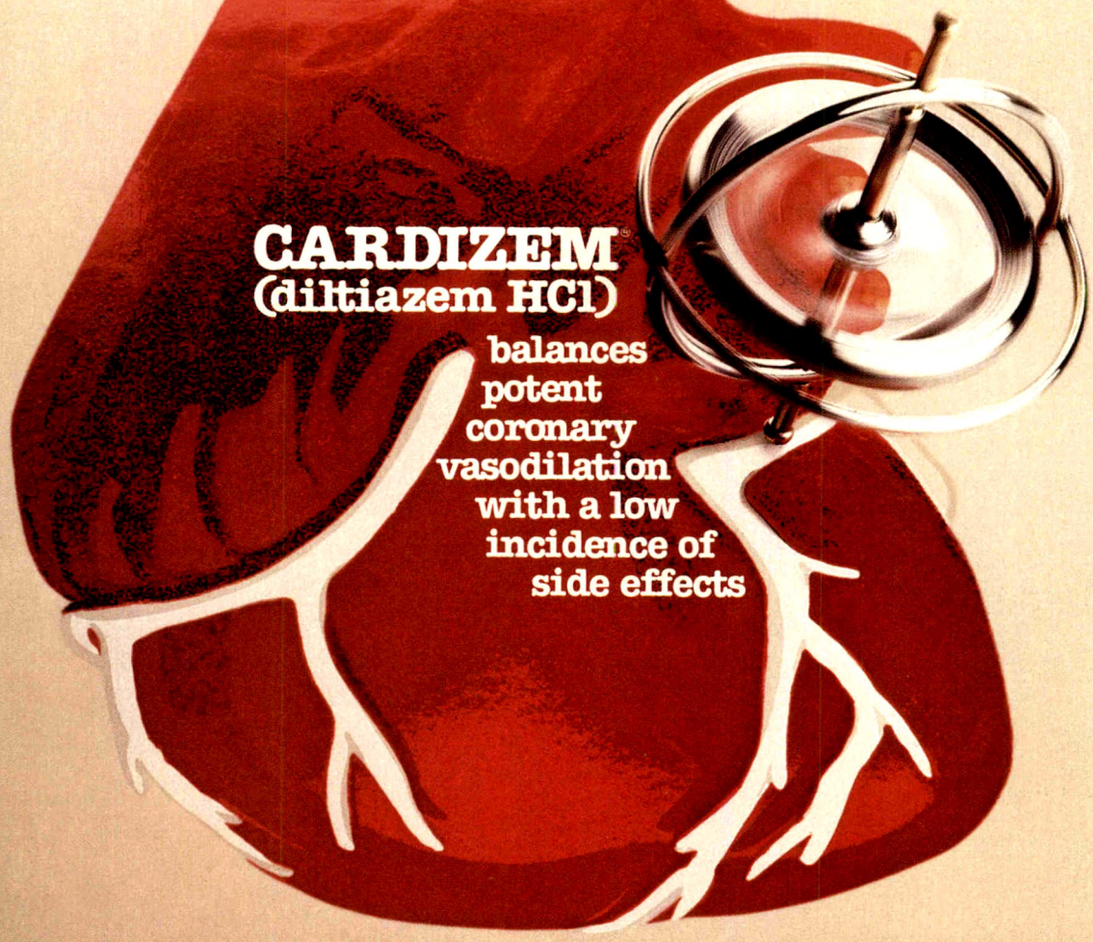

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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

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In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

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PROFESSIONAL USE INFORMATION

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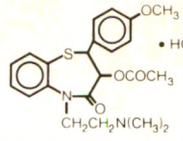
DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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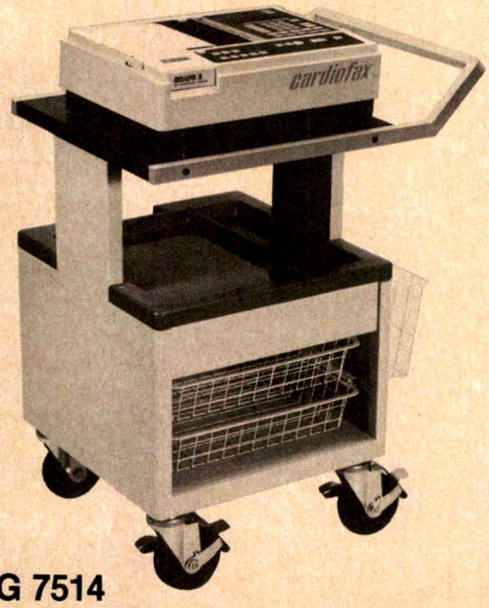

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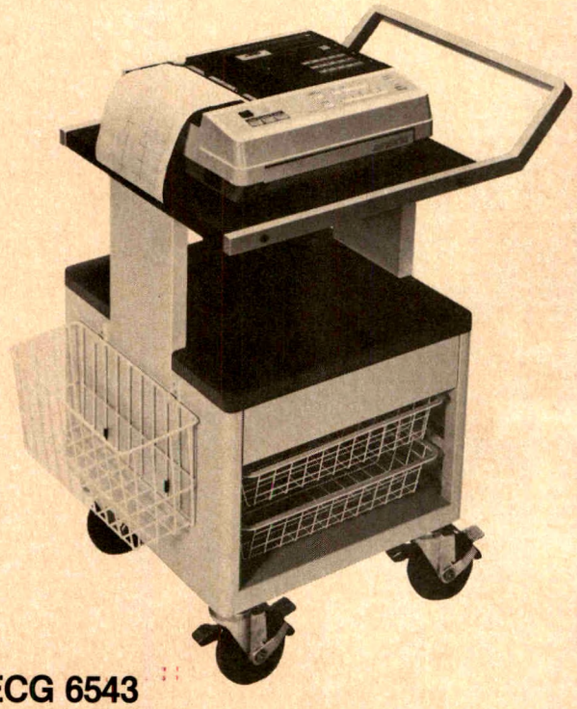

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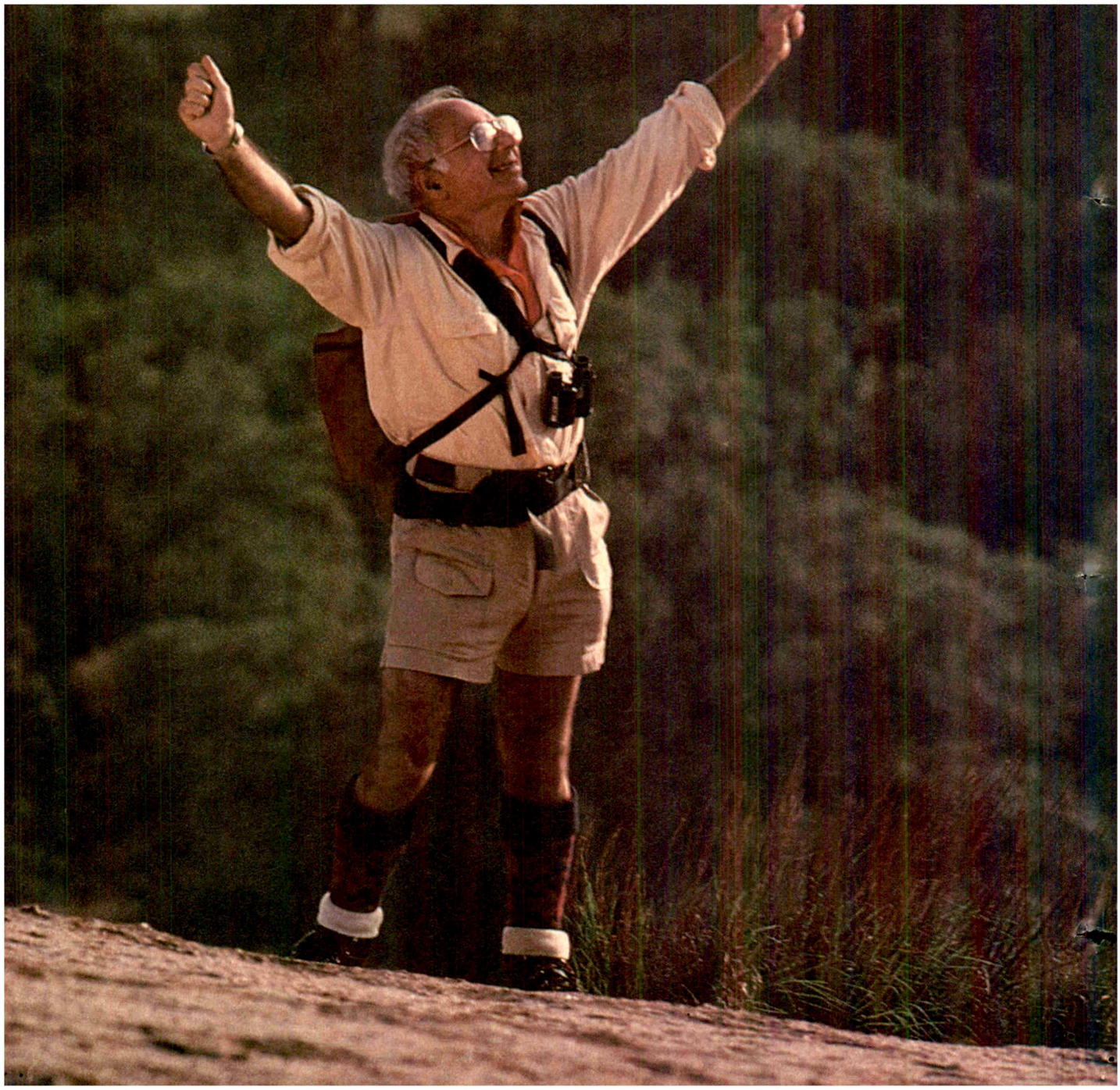

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continuous to pulsed delivery at repetition rates of 1 Hz to 256 MHz, pulse duration of 0.2 to 358 ns, and pulse energies of 2 nJ to 370 mJ. Gross and light microscopic signs of thermal injury were eliminated by pulsed delivery at low repetition rates (less than 200 Hz) and high pulse energies (greater than 10 mJ).

667 **Effects of Hematoporphyrin Derivative and Photodynamic Therapy on Atherosclerotic Rabbits**

FRANK LITVACK, WARREN S. GRUNDFEST, JAMES S. FORRESTER, MICHAEL C. FISHBEIN, H.J.C. SWAN, ELIOT CORDAY, DAVID M. RIDER, I. STEWART McDERMID, THOMAS J. PACALA, and JAMES B. LAUDENSLAGER

This study was performed to confirm the selective uptake of hematoporphyrin derivative (HPD) within atheroma, to localize the site of uptake of HPD within the atheroma and to determine the potential for photodynamic therapy of atherosclerosis in the rabbit model. In 10 atherosclerotic rabbits that received HPD intravenously, all had HPD uptake within atheroma, but not within normal intima. Fluorescence microscopy revealed a diminishing concentration gradient of HPD from intimal surface layers inwards. Eight rabbits received from 5 to 20 mg/kg of HPD and photodynamic therapy with 636-nm red light. At 3 hours after irradiation there was no effect, but at 1 and 2 weeks some rabbits had less atheroma in treated segments than in controls. Histologic examination of treated segments revealed smooth muscle concentration near the intima, but similar findings occurred in some apparently nonirradiated areas.

672 **Effect of Intracoronary Verapamil on Infarct Size in the Ischemic, Reperfused Canine Heart: Critical Importance of the Timing of Treatment**

HUEY-MING LO, ROBERT A. KLONER, and EUGENE BRAUNWALD

To determine whether the beneficial effect of calcium blocking drugs occurs only during ischemia or during reperfusion as well, anesthetized dogs were subjected to 3 hours of occlusion of the left anterior descending coronary artery followed by 3 hours of reperfusion. In protocol A, intracoronary verapamil was begun 90 minutes after coronary occlusion and continued for 1 hour into reperfusion, while a control group received an infusion of saline solution. Area of necrosis, expressed as a percent of area at risk, was smaller in the verapamil group (29 ± 8%) than in the controls (57 ± 8%, $p < 0.05$). In protocol B, in which intracoronary verapamil was begun 5 minutes before blood reperfusion and continued throughout the 3 hours of reperfusion, there was no reduction of infarct size. Therefore, calcium blockade of ischemic myocytes delays death and enhances salvage produced by reperfusion. However, calcium blockade begun after prolonged coronary occlusion does not enhance reperfusion-induced myocardial salvage.

677 **Sudden Death and Experimental Acute Myocardial Infarction**

YVETTE TROLESE-MONGHEAL, PIERRE DUCHENE-MARULLAZ, JEAN-FRANCOIS TROLESE, MICHEL LEINOT, JEAN-CLAUDE LAMAR, and PIERRE LACROIX

Ligature of the anterior descending coronary artery in 658 dogs was fatal within 1 hour in 12% of the cases (instantaneous death) and within 24 hours in 25% of the cases (sudden death). Percentage of sudden death was proportional to the logarithm of the weight of the dogs in the range studied. Sudden death rate varied widely when small series of dogs were considered. Only with at least 50 to 60 dogs per series were reproducible figures obtained. Hence, reliable assessment of preventive action of drugs can only be made if experimental series of at least this size are used.

681 **Effect of Pulmonary Artery Distention on Systemic Vascular Resistance in Newborn Lambs**

JAY M. MILSTEIN and BOYD W. GOETZMAN

Acute distention of the left pulmonary artery in newborn lambs causes statistically significant increases in both systemic vascular resistance and aortic pressure. It is postulated that such changes may be important in affecting redistribution of cardiac output in the fetus, but they are probably too small to explain the elevated systemic vascular resistance observed in some infants with persistent fetal circulation.

CONGESTIVE HEART FAILURE

685 **Pharmacokinetics and Pharmacodynamics of Milrinone in Chronic Congestive Heart Failure**

JOSEPH R. BENOTTI, LAWRENCE J. LESKO, JANE E. McCUE, and JOSEPH S. ALPERT

The pharmacokinetics and hemodynamic effects of milrinone administered in an ascending intravenous bolus schedule were studied in patients with advanced congestive heart failure. Each dose affected prompt but very short-lived increases in cardiac output and stroke work and decreases in pulmonary artery pressure, right atrial pressure and systemic and pulmonary vascular resistance in a non-dose-dependent fashion. Milrinone kinetics

Continued on page A49

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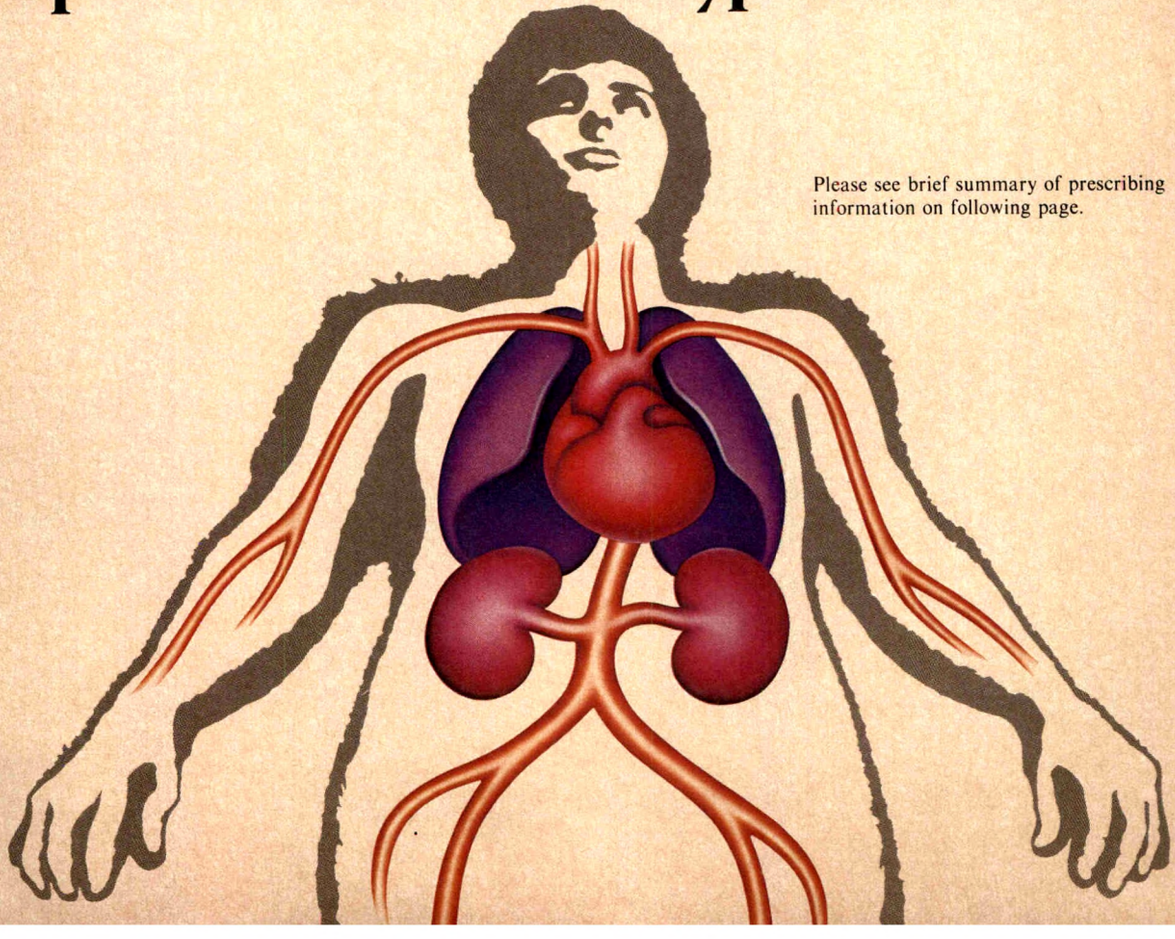

Please see brief summary of prescribing information on following page.

NORMODYNE®

brand of labetalol hydrochloride

Tablets

BRIEF SUMMARY

INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS

Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

PRECAUTIONS

General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600
Number of Patients	522	181	606	608
Dizziness (%)	2	3	3	3
Fatigue	2	1	4	4
Nausea	<1	0	1	2
Vomiting	0	0	<1	<1
Dyspepsia	1	0	2	1
Paresthesias	2	0	2	2
Nasal Stuffiness	1	1	2	2
Ejaculation Failure	0	2	1	2
Impotence	1	1	1	1
Edema	1	0	1	1

Labetalol HCl Daily Dose (mg)	800	900	1200	1600	2400
Number of Patients	503	117	411	242	175
Dizziness (%)	5	1	9	13	16
Fatigue	5	3	7	6	10
Nausea	4	0	7	11	19
Vomiting	<1	0	1	2	3
Dyspepsia	1	0	2	2	4
Paresthesias	1	1	2	5	5
Nasal Stuffiness	2	2	4	5	6
Ejaculation Failure	3	0	4	3	5
Impotence	2	4	3	4	3
Edema	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes Dry eyes.

Immunological System Antimitochondrial antibodies.

Liver and Biliary System Cholestasis with or without jaundice.

Musculo-Skeletal System Muscle cramps; toxic myopathy.

Respiratory System Bronchospasm.

Skin and Appendages Rashes of various types, such as generalized maculo-papular lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block. See **CONTRAINDICATIONS.**

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a beta$_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered tid may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg bid.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED

NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).

NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.

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Kenilworth, NJ 07033

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The Q55 TREADMILL is included and provides 350-lb. patient capacity, 1–10 mph speed range, 0–25% grade range, and automatic calibration, self-test and trouble monitoring.

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- COMPREHENSIVE DISPLAYS—6 seconds of live ECG data, resting and current averaged beats, split screen freeze, tabular and graphic displays, continuous write from memory, digital displays of heart rate, ST parameters, and stage and time data.
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Clinical Clues to MIXED ANGINA *No. 1*

Thirty seconds ago he was reading

He wasn't exercising; his myocardial oxygen demand didn't increase. Yet now he's having an angina attack.

That's the unpredictability of MIXED ANGINA—vasoconstriction coexisting with fixed coronary lesion, to produce a critical reduction of myocardial blood flow.

And because vasoconstriction is an unpredictable event, ischemia and pain occur unpredictably:

- at rest, or even during sleep
- at varying levels of exercise
- upon exposure to cold
- under emotional stress
- diurnally, typically in the morning

PROCARDIA® (nifedipine) is a primary therapy for the patient with MIXED ANGINA. It prevents vasoconstriction in both large coronary arteries and coronary arterioles to maintain myocardial blood flow and oxygen supply. At the same time, PROCARDIA dilates peripheral arteries to reduce afterload and myocardial oxygen demand.

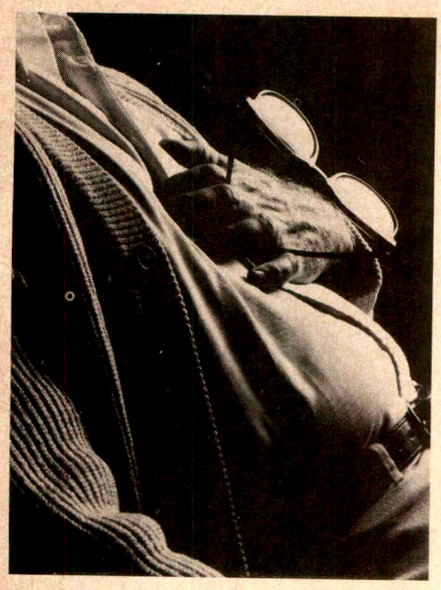
As a result, PROCARDIA can significantly reduce your patient's angina attack rate and need for nitroglycerin.[1]

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Primary Protection in
MIXED ANGINA

Please see PROCARDIA® (nifedipine) brief summary on next page.

Thirty seconds ago he was reading.



PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PRIMARY PROTECTION IN MIXED ANGINA

Usual Effective Dosage: 30 to 60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases.

A Favorable Safety Profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

Reference:

1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 106:644-652, 1983.

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA (nifedipine) therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA patients. No clinical significance for these findings has been demonstrated.

Although PROCARDIA has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to PROCARDIA therapy is uncertain in most cases but probable in some.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, mice and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cramps, flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, gingival hyperplasia, and erythromelalgia. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related: Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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Pfizer

LABORATORIES DIVISION
PFIZER INC.

conformed to an open 2-compartment model of drug distribution and elimination. The elimination half-life of milrinone is such that bolus administration is required for rapid hemodynamic efficacy. However, hemodynamic effects should resolve promptly with discontinuation of milrinone therapy.

690 **Effects of Hydralazine on Pressure-Volume and Stress-Volume Relations in Congestive Heart Failure Secondary to Idiopathic Dilated Cardiomyopathy**
MARK L. SMUCKER, C. FAGG SANFORD, and KIRK M. LIPSCOMB

The mechanism by which hydralazine improves cardiac function in patients with heart failure is not well characterized. Hydralazine may improve left ventricular (LV) function by decreasing afterloading LV wall stress or by increasing myocardial contractility. The effect of intravenous hydralazine was assessed in 8 patients with severe idiopathic dilated cardiomyopathy. Hydralazine increased stroke volume index and ejection fraction and decreased systemic vascular resistance and LV stress. Patients with high LV wall stress had higher LV end-diastolic pressure, higher LV end-diastolic volume index, lower ejection fraction and higher systemic vascular resistance than patients with normal LV stress. LV wall stress decreased more in patients with high LV stress, because hydralazine decreased systolic pressure and diastolic pressure or volume in those patients. Late systolic portions of pressure-volume loops in patients with normal LV stress suggested increased myocardial contractility, but this was not confirmed by LV dP/dt. Hydralazine improves LV function in patients with dilated cardiomyopathy by reducing elevated LV wall stress.

BRIEF REPORTS

697 **Left Ventricular Apical Masses: Noninvasive Differentiation of Rare from Common Ones**
ANDRE KEREN, TOSHIHIKO TAKAMOTO, DONALD C. HARRISON, and RICHARD L. POPP

699 **Pericardial Defect Mimicking a Left Atrial Mass**
BARRY S. TALESNICK, FREDERICK J. SUTTON, YU-CHEN LEE, and JOSEPH S. McLAUGHLIN

700 **Mitral Valve Prolapse, Wolff-Parkinson-White Syndrome, His Bundle Sclerosis and Sudden Death**
XAVIER ANDRÉ-FOUËT, AHMIADZIAH TABIB, PHILIPPE JEAN-LOUIS, DIDIER ANNE, PAUL DUTERTRE, CHRISTIAN GAYET, ALAIN HUYGUE de MAHENGE, ROBERT LOIRE, and MAURICE PONT

AJC 25 YEARS AGO

701 **The AJC in October 1960**
RICHARD E. CLARK

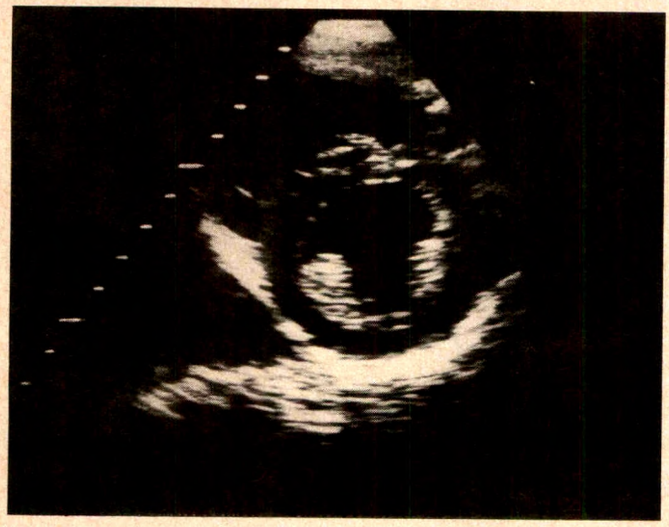
703 **FROM THE EDITOR**

704 **LETTERS**

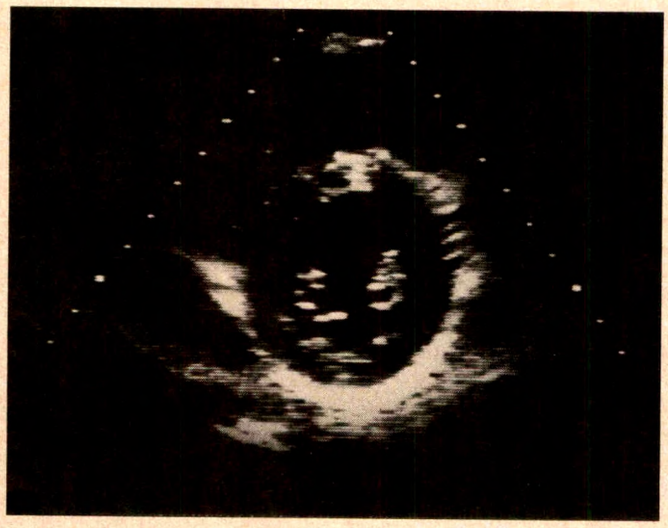
INSTRUCTIONS TO AUTHORS on page 622

BOOKS RECEIVED on page 696

The only difference in Cardioscan's image is the cost.



$25,000 Cardioscan's affordable image looks like this.



$90,000 At more than three times the cost of Cardioscan, their image looks the same.

Until now, sophisticated, high-resolution echocardiography came with a high price tag. To get images like the one at the top you had to pay the cost at the bottom. Interspec has changed all that. We developed Cardioscan™—the easy-to-use echocardiography system that makes high-quality ultrasound imaging not only possible, but *affordable.*

Unlike other low-cost systems, Cardioscan doesn't sacrifice performance for price. You get all the advantages of larger, hospital-scale units—plus, some features often not available even on more expensive systems.

And, Cardioscan has been designed with the future in mind. You do not have to be concerned about your system becoming obsolete as echocardiographic technology advances or your clinical needs change. Your system will be fully upgradeable to keep pace with the demands of your practice.

The best technology packaged in a lightweight, compact design

There is only one way to understand the quality Cardioscan delivers. And that is to compare it with other units. Even when judged against systems costing three times as much, Cardioscan more than measures up.

More reasons to decide on Cardioscan

- Superior image quality and resolution in both 2-D and M-mode.
- Logically grouped, easy-to-learn controls let you concentrate on the patient, not the instrument.
- On-line or off-line calculations capability means calculations and annotations can be performed during patient examinations, or later *in video playback.*
- Triple image memory means you can store up to three images and select the preferred one for calculations and/or hard copy.

- ECG with dual trigger enables automatic viewing of end-systolic and end-diastolic images from the same cardiac cycle.
- Small, lightweight transducer available in a variety of frequencies and focal zones helps make Cardioscan adaptable to a wide range of applications.

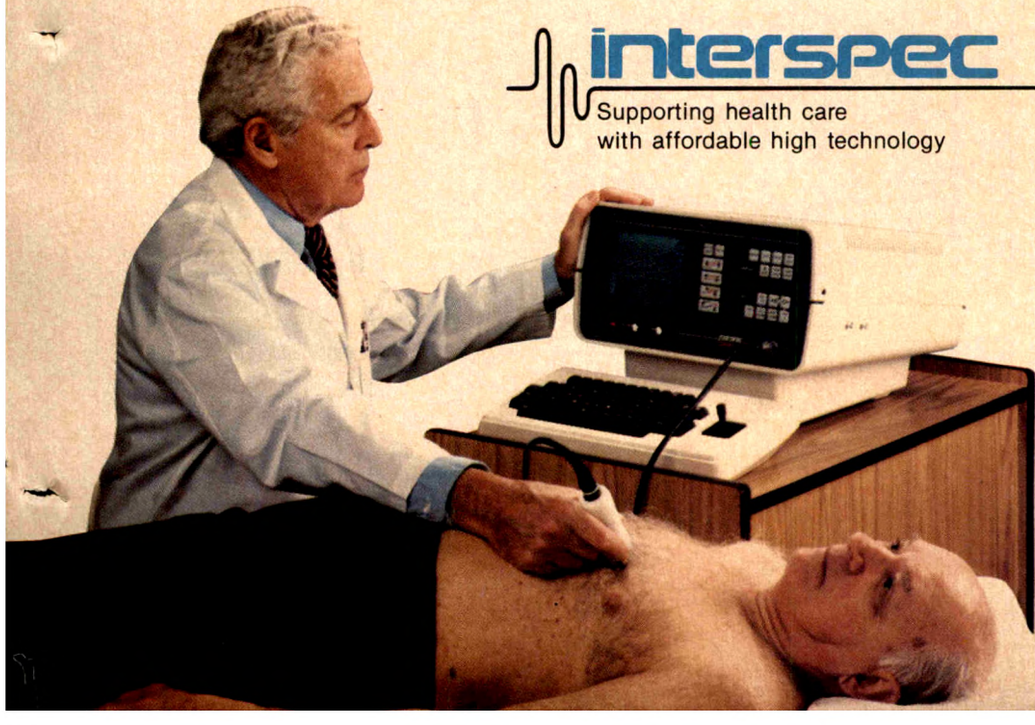
The Cardioscan Doppler

In keeping with Interspec's commitment to cardiology, Cardioscan has been designed to accept major upgrades. One of the first of these is the Cardioscan Doppler, which adds noninvasive hemodynamics to your diagnostic capabilities. With pulsed, high PRF, continuous wave and comprehensive calculations, this Doppler is truly state-of-the-art.

Reliable service

Because Cardioscan is made in the U.S., availability of parts is never a problem. A complete service policy includes rapid response to calls and a loaner program to assure maximum up-time.

Compare our image. Compare our price.
Compare our features.
Then contact Interspec today.



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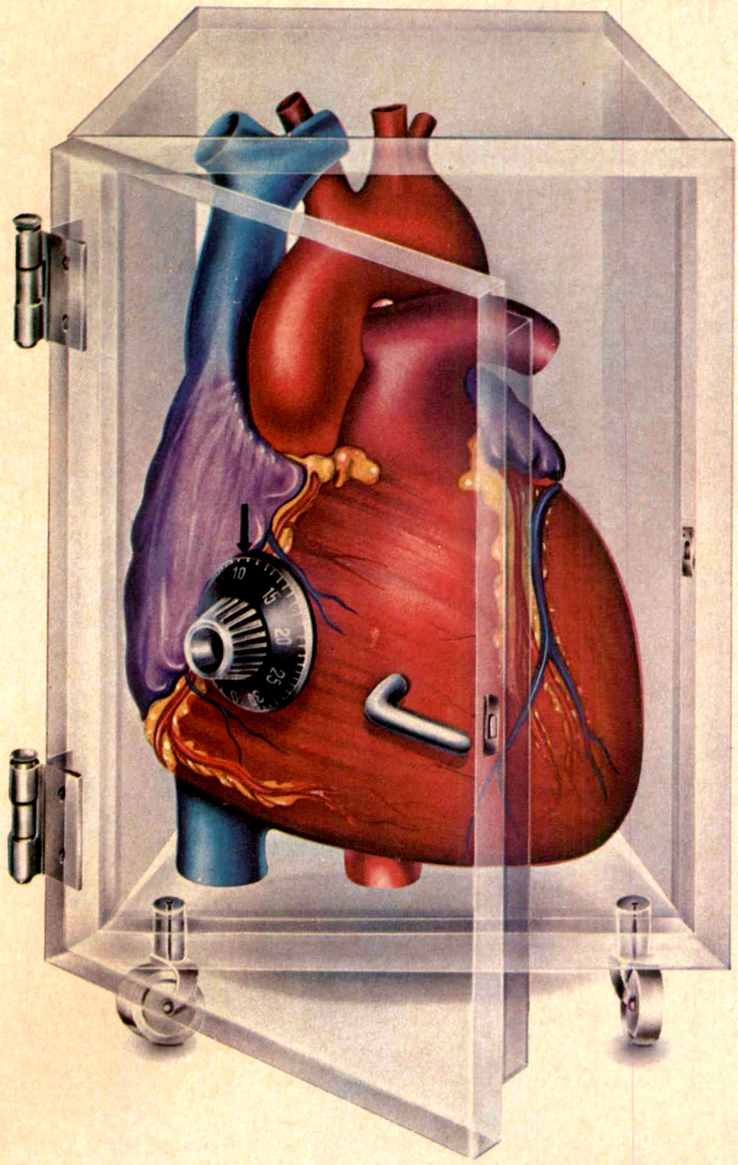
In hypertension... the risks of some diuretics or the protection of Lopressor



Safe from complications due to diuretic-induced K+loss

Unlike some diuretics, Lopressor does not waste potassium or cause hypokalemia which has been implicated in cardiac arrhythmias. Some diuretic therapy requires professional monitoring for potassium depletion.

Excellent safety record

Lopressor is generally well tolerated. Shortness of breath and bradycardia have occasionally been reported. Cardioselectivity* offers an added margin of safety compared to nonselective beta blockers.

A safe bet for compliance

The combination of once-a-day dosage and good tolerability makes a Lopressor regimen easy for patients to stay with.

*Exerts a relative preference for beta-one receptors; this preference is not absolute.

Contraindicated in heart block greater than first degree, sinus bradycardia, cardiogenic shock, and overt heart failure. Side effects with Lopressor are generally mild and transient, the most common being tiredness, dizziness, depression, and diarrhea.

Please see next page for Brief Summary of Prescribing Information.

Lopressor®

metoprolol tartrate

Tablets: 50 mg, 100 mg
Ampuls: 5 mg/5 ml
Prefilled Syringes: 5 mg/5 ml

Changing the Course of Cardiovascular Care

Geigy

536-2998-A

Lopressor®
metoprolol tartrate

C84-38 (Rev. 7/85)

Tablets
Ampuls
Prefilled Syringes

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.
Myocardial Infarction
Lopressor ampuls, prefilled syringes and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Hypertension
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; significant heart block greater than first degree (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice (see **PRECAUTIONS, Information for Patients**).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness. Patients should contact the physician if any difficulty in breathing occurs, and before surgery of any type, the patient should inform the physician or dentist that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a 1-year study in dogs, there was no evidence of drug-induced toxicity at or below oral dosages of 105 mg/kg per day. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.
Pregnancy Category B
Reproduction studies have been performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg and have revealed no evidence of impaired fertility or teratogenicity due to Lopressor. Increased postimplantation loss and decreased neonatal survival did occur in the rats (threshold between 50 and 500 mg/kg), and distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported, but a drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; and congestive heart failure have been reported. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) has been reported in fewer than 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100, or fewer, patients.

Hypersensitive Reactions: Pruritus has occurred in fewer than 1 of 100 patients. Rash has been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Alopecia has been reported.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

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Simultaneous Computer Mapping to Facilitate Intraoperative Localization of Accessory Pathways in Patients with Wolff-Parkinson-White Syndrome

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Sixteen patients with the Wolff-Parkinson-White syndrome underwent simultaneous intraoperative computer mapping from multiple sites before surgical division of the accessory pathways. A 16-bipolar electrode band was positioned around the atrioventricular groove. Ventricular epicardial electrograms from single beats were recorded simultaneously during atrial pacing, resulting in maximal preexcitation, and atrial electrograms were recorded during orthodromic supraventricular tachycardia. Four-level transmural plunge needle electrodes were used concomitantly in 3 patients. Electrograms were processed separately using a guarded signal conditioner that isolates, amplifies, filters and analog-to-digitally converts synchronously at 2 kHz with 12-bit accuracy. Digital data were transmitted by fiber optics to a high-density digital recorder and processed with a computer having rapid interactive graphics. Results in the 16 patients revealed 20 distinct Kent bundles. Two patients had only nonsustained supraventricular tachycardia induced intraoperatively and 1 patient manifested intermittent anterograde ventricular preexcitation. Multiple pathways were identified in 4 patients. This simultaneous multiple electrode mapping procedure facilitates intraoperative mapping by requiring only a single beat for analysis of anterograde and retrograde activation times, decreases cardiac manipulation during mapping and obviates the need for cardiopulmonary bypass, and permits analysis of transmural activation patterns. This approach decreases markedly the time required for mapping and permits accurate study of nonsustained arrhythmias as well as rapid identification of multiple accessory pathways.

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Surgical division of accessory atrioventricular (AV) pathways has been shown to be effective and safe for the treatment of symptomatic patients with the Wolff-Parkinson-White syndrome.[1–4] The success of surgical therapy depends on accurate localization of the accessory pathway. Intraoperative mapping is performed to define precisely the atrial and ventricular insertion sites of the accessory pathways and to detect additional accessory pathways that may not have been readily apparent preoperatively. Conventional intraoperative mapping procedures involve the sequential assessment

TABLE I Clinical Profile

No. of pts	16
Age range (yr)	4 to 50
Sex (M/F)	6/10
Pathway location	
Left free wall	12
Right free wall	2
Posterior septal	6
Pts with multiple accessory pathways	
Multiple	4
Single	12

of ventricular and atrial epicardial activation patterns by a single-bipolar probe during stable ventricular preexcitation and sustained orthodromic supraventricular tachycardia, (SVT), respectively.[5–7] The conventional approach has been limited by the time required to complete mapping and the associated hemodynamic compromise that often accompanies induction of SVT, necessitating prolonged cardiopulmonary bypass time and the requirement of a uniform sustained arrhythmia. In addition, extensive cardiac manipulation, particularly during mapping of the posterior aspect of the heart, may result in a change in QRS and delta wave configuration, further hemodynamic embarrassment and inability to maintain a sustained SVT.

Recently, we developed a computerized mapping system that allows for simultaneous acquisition, storage and analysis of multiple epicardial, intramural and endocardial electrograms derived from a single depolarization of the heart.[8] To obviate the limitations of conventional procedures, we performed simultaneous computer mapping intraoperatively in patients with Wolff-Parkinson-White (WPW) syndrome referred for surgical treatment. We first selected patients with WPW syndrome to assess the clinical applicability of the computer mapping system, since the pathogenesis of this disorder has been well characterized.

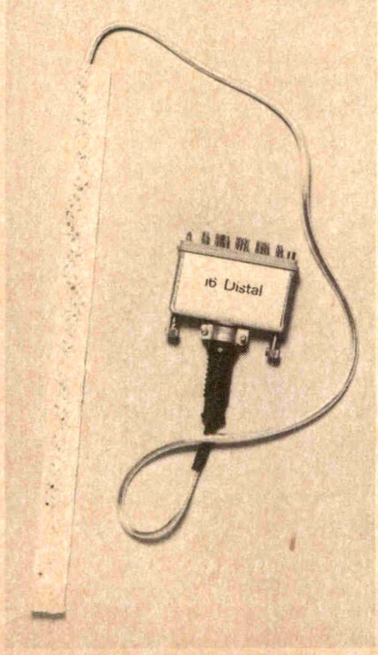

FIGURE 1. Epicardial band containing 16 bipolar button electrodes.

Methods

Patients: Sixteen patients with WPW syndrome referred to Barnes Hospital for surgical division of their accessory pathways were studied intraoperatively with the computer mapping system. Each patient had recurrent episodes of sustained orthodromic SVT, atrial fibrillation, or both. Each patient was studied preoperatively in the Barnes Hospital Electrophysiology Laboratory using standard catheter techniques.[9] Pertinent clinical characteristics of the patients are summarized in Table I. Eighteen accessory pathways were identified in the 16 patients during the preoperative electrophysiology study. Two additional pathways were identified during computer mapping intraoperatively.

Mapping procedure: Computer mapping was performed in each patient after induction of anesthesia, exposure of the heart through a median sternotomy and cannulation of the great vessels, but before institution of cardiopulmonary bypass. A nylon mesh band with 16 bipolar button electrodes (Fig. 1) was positioned around the AV groove. The electrode buttons had an interpole spacing of 0.6 mm and rested lightly on the epicardial surface of the heart. The distance between electrode buttons was 1 cm. Positioning of the band required only minimal cardiac manipulation and, once moist, remained adherent to the epicardium. Anterograde ventricular activation was assessed first during maximal ventricular preexcitation with the band array located below the anular fibrosis. Pacing from the atrium ipsilateral to the accessory pathway was used to facilitate preexcitation. Decisions regarding pacing site and rate of pacing were based on results of the preoperative electrophysiology study. If multiple pathways were suspected preoperatively or intraoperatively, pacing from multiple atrial sites was performed and anterograde ventricular activation assessed. The electrode band was moved superiorly to the atrium. Retrograde atrial activation was then assessed during orthodromic SVT. In 1 patient, only isolated AV echo beats were observed intraoperatively and sustained orthodromic SVT could not be induced. Mapping from multiple atrial sites simultaneously was performed during isolated AV echo beats. After institution of cardiopulmonary bypass, single-probe mapping was performed in the first 4 patients to confirm the findings of the computer analysis and in 5 patients who had posterior septal pathways as an adjunctive technique for endocardial mapping. In 3 patients who had left free wall pathways localized by the band technique, 4 plunge needle electrodes containing 4 bipolar pairs per needle were inserted at the site of the ventricular insertion of the accessory pathway and on either side of the anomalous connection. Interpole spacing was 500 μm and each bipole was separated by 2.5 mm, with the proximal bipole pair located 500 μm from the epicardial surface. The transmural pattern of ventricular activation was assessed during a maximally preexcited beat.

Data processing and analysis: The computer system used was recently described in detail.[8] The system was designed to accumulate simultaneous information from multiple intracardiac locations and to facilitate rapid and accurate analysis of the data.

Bipolar electrogram information obtained from epicardial and intramural electrodes, along with electrocardiographic data, were sampled at 2 kHz, individually amplified, filtered (40 to 500 Hz), and digitized using a portable operating room cart specially designed for this purpose. The output of each amplifier was sequentially strobed at 500 kHz, converted from parallel to serial and transferred in a 12-bit digital format through a fiberoptic digital transmission system to the remote computer facility located approximately 1,000 yards from the

operating suite. The data were then converted back from a serial to parallel format and stored on a Sangamo-Weston Sabre IV high-density recorder, from which desired data segments were analyzed. A 2-way audio transmission and analog electrocardiographic data also accompanied the digital data stream from the operating room to the computer facility.

Data analysis was performed in several automated steps using a PDP 11/34A (Digital Equipment Corp.) computer equipped with high-resolution graphic capabilities. Once the appropriate beats had been recorded, the electrocardiogram was scanned and a time window of variable length chosen to examine depolarization sequences of interest. During assessment of anterograde ventricular activation, the time window was positioned at the onset of the delta wave and incorporated the QRS complex. During assessment of retrograde atrial activation during either sustained orthodromic SVT or an AV echo beat the time window was positioned at the end of the QRS complex and incorporated the retrograde P wave. Each electrogram was autocalibrated and displayed along with a computer-chosen activation time based on a peak criterion.[6,10] Earliest sites of activity and their relation to the delta wave or retrograde P wave were used to pinpoint ventricular and atrial insertion sites of the Kent fibers, respectively. The electrographic information and activation times were available instantaneously in the operating room, which was equipped with a color graphic display similar to that located in the computer facility.

Results

Simultaneous intraoperative computer mapping facilitated accurate localization of accessory pathways and afforded several other advantages over conventional procedures. A representative retrograde atrial activation map during orthodromic SVT is shown in Figure 2. Earliest retrograde atrial activation occurred 27 ms after the beginning of the time window and was located at a left posterolateral site. The remaining sites are activated in a sequential, orderly fashion confirming the presence of a single accessory pathway.

Single probe epicardial mapping was performed in the first 4 patients to validate activation patterns determined using the computer mapping system. In these

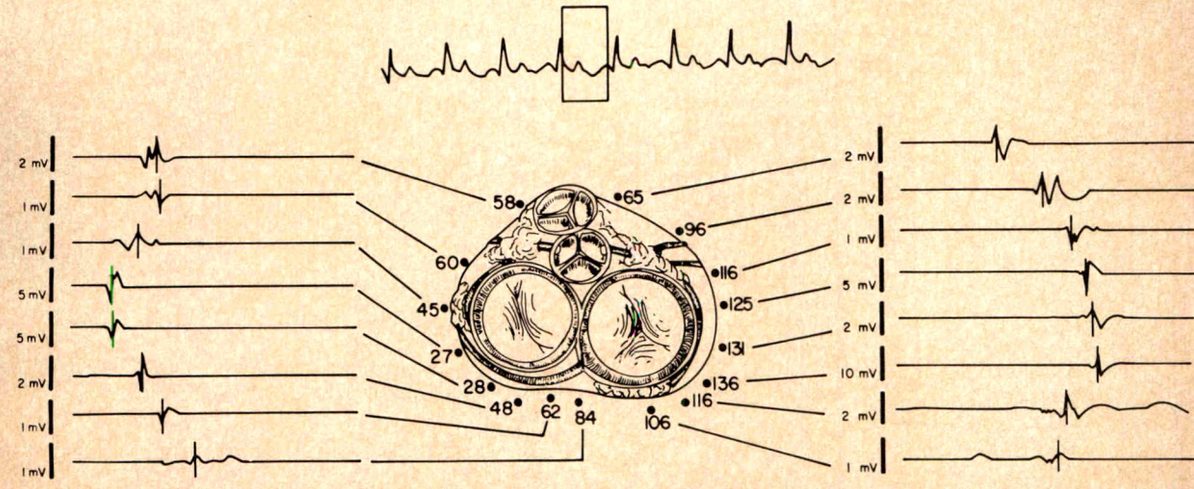

FIGURE 2. Retrograde atrial epicardial activation times during sustained orthodromic supraventricular tachycardia. The electrocardiogram, time window and atrial epicardial electrograms are shown. **Numbers** on the **left** of each recording refer to a peak-to-peak amplitude scale after autoranging of the individual electrograms. The **vertical cursor** represents the computer-derived activation time at each electrode site. In this example, a single left free wall pathway is apparent. Earliest atrial activity was recorded 27 ms after the onset of the time window.

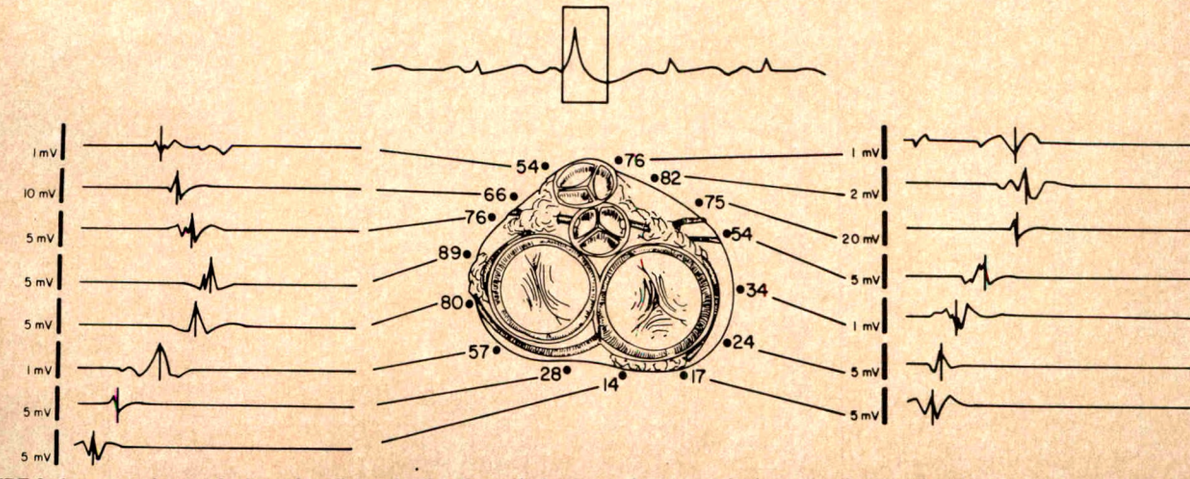

FIGURE 3. Anterograde ventricular epicardial activation times during intermittent ventricular preexcitation. The electrocardiogram shows a single preexcited beat. The activation map indicates the presence of a right-sided paraseptal bypass tract.

patients, the results of the single hand-held probe study localized the accessory pathway to the same site identified by the computer mapping system. However, the conventional approach required cardiopulmonary bypass, prolonged atrial pacing and sustained orthodromic SVT, considerable cardiac manipulation, and 30 to 40 minutes to acquire and accurately analyze the data.

During computer mapping, however, only a single beat of the SVT was required for atrial activation times. As a result, the episode of SVT was terminated after only several beats, obviating the need for cardiopulmonary bypass during the mapping procedure. Complete atrial and ventricular mapping and data analysis can be completed in approximately 10 minutes.

Accurate localization of accessory pathways manifesting intermittent conduction has heretofore been difficult and frequently impossible. Simultaneous mapping, in which localization can be made on the basis of a single beat, obviates this difficulty. Figure 3 shows intermittent ventricular preexcitation. Simultaneous mapping of multiple ventricular sites around the AV groove during a single preexcited beat reveals a right posterior paraseptal pathway activating 14 ms after the onset of the time window. A second relatively early zone of activation observed anteriorly (54 ms) is most likely the result of anterograde conduction through the accessory pathway and normal His-Purkinje system. The results of atrial mapping during sustained orthodromic SVT revealed a single right paraseptal pathway. After dissection of the posterior septal space, preexcitation was no longer present and orthodromic SVT could no longer be induced. Retrograde atrial mapping during intermittent conduction over a concealed accessory pathway from another patient is illustrated in Figure 4. This patient manifested incessant SVT owing to a concealed posterior septal accessory pathway. During surgery, however, only frequent AV echo beats occurred and sustained SVT could not be induced. Analysis of P-wave morphology using multiple electrocardiographic leads was identical to that observed preoperatively during SVT. Mapping of a single AV echo beat confirmed a posteroseptal concealed accessory pathway. Dissection of the posteroseptal space eliminated SVT postoperatively. Multiple accessory pathways may be suspected preoperatively, but require extensive and laborious intraoperative mapping using conventional procedures. The results of simultaneous mapping from multiple ventricular sites during ventricular preexcitation in a patient suspected of having 2 distinct accessory pathways during the preoperative electro-

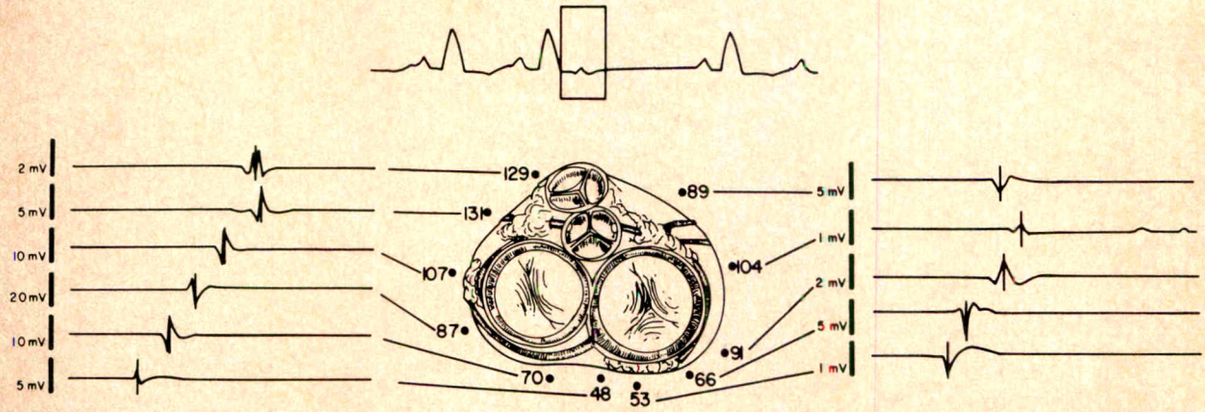

FIGURE 4. Retrograde atrial epicardial activation times during a single atrioventricular echo beat. The accessory pathway was located in the posterior septum.

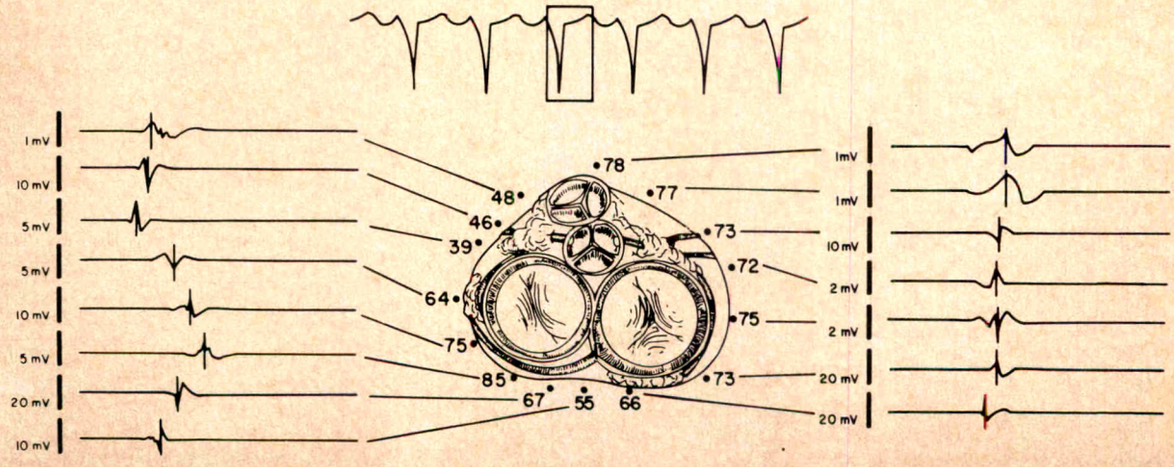

FIGURE 5. Anterograde ventricular epicardial activation showing 2 distinct accessory pathways (left anterolateral and posteroseptal).

physiology study are shown in Figure 5. Analysis of ventricular activation times revealed 2 distinct early sites of activation occurring 39 and 55 ms after the onset of the time window corresponding to a left anterolateral and a posteroseptal location, respectively. Activation of the right ventricle results from impulse propagation clockwise and counterclockwise from these 2 sites and accounts for the poor progression of activation times along the right AV groove. Thus, rapid identification of these 2 accessory pathways was facilitated by simultaneously recording from multiple sites.

Transmural ventricular activation during ventricular preexcitation is illustrated in Figure 6, from a patient in whom a left paraseptal pathway had been localized by the band mapping technique. Two plunge needles located near the left paraseptal tract (electrodes C and D) showed earliest activation at a subepicardial location with reversal of the normal endocardial to epicardial activation patterns. However, the 2 plunge electrodes located at adjacent sites (electrodes A and B) show normal endocardial to epicardial activation. This phenomenon, observed in each of the 3 patients studied in which transmural recordings were obtained, verified the epicardial location of the left free wall Kent bundles.

Discussion

The present report is a summary of our experience using simultaneous epicardial and transmural mapping of the AV groove for rapid and accurate localization of accessory pathways. Simultaneous epicardial mapping of the AV groove affords several distinct advantages over conventional single-probe analysis. First, the band technique offers accurate and rapid identification of accessory pathways and obviates the need for cardiopulmonary bypass during cardiac mapping. Both the ventricular and atrial insertion sites can be identified rapidly using anterograde and retrograde maps. Second, this approach promotes stable pathway conduction by reducing the need for extensive cardiac manipulation during mapping. Third, accurate mapping can be completed during intermittent conduction over the accessory pathway. Fourth, in cases of multiple accessory pathways, distinct pathways can be discerned from a single beat (Fig. 5) or when multiple pacing sites are required to elicit conduction over alternate pathways, several maps can be obtained rapidly.

Previous reports have detailed computer-assisted mapping techniques used to facilitate intraoperative localization of accessory pathways.[6] Techniques for simultaneous multisite mapping have also been reported, including sock arrays[11] and a 4-probe glove.[12] However, the clinical value of these methods has not been documented thoroughly. Band mapping of the AV groove provides a complete assessment of the areas of concern without the need for cumbersome electrode arrays and time-consuming electrode localization procedures. Furthermore, the resolution afforded by the technique is readily expandable because as many as 240 sites can be assessed simultaneously using our current system configuration.

The band mapping technique has no associated morbidity other than that associated with the operation itself. Two potential drawbacks to selective mapping of the AV groove have been discussed previously.[6] First, the presence of abundant epicardial fat in this location can obscure definitive electrical recordings. In this case, the band can be easily repositioned inferiorly to lie further below the AV groove. The other potential problem associated with selective mapping of the AV groove is the unusual occurrence of Mahaim or nodoventricular fibers causing preexcitation. These fibers characteristically have ventricular insertions well below the AV groove. When Mahaim fibers are suspected

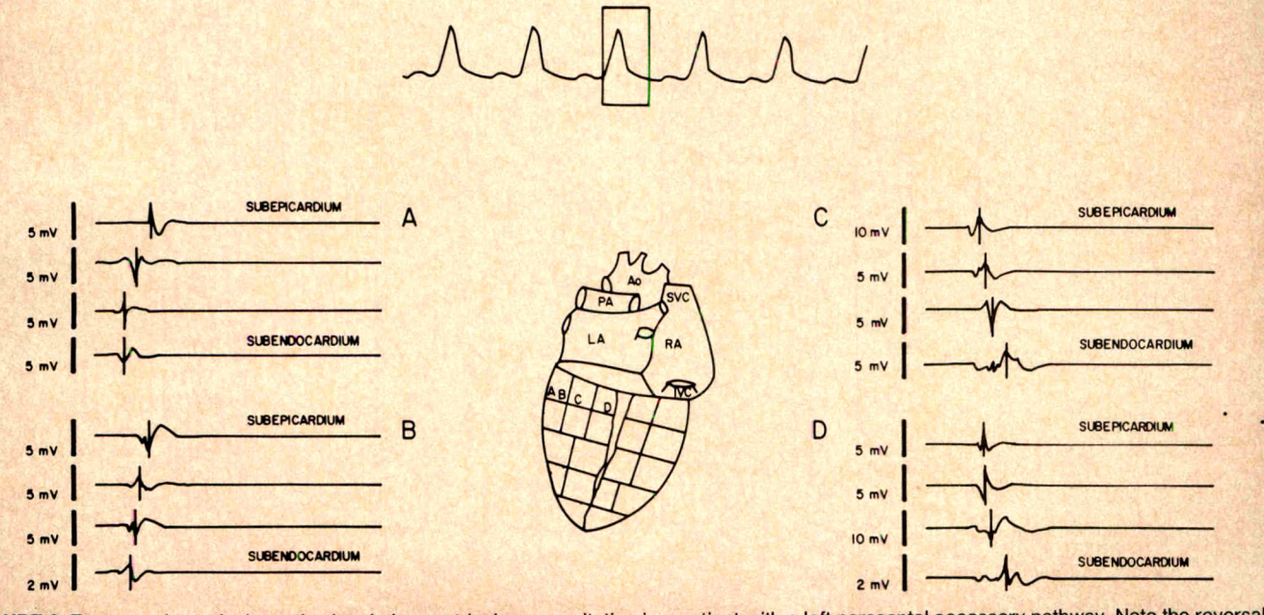

FIGURE 6. Transmural ventricular activation during ventricular preexcitation in a patient with a left paraseptal accessory pathway. Note the reversal of the normal endocardial to epicardial activation pattern recorded from electrodes C and D positioned at the site of ventricular insertion. Normal (endocardial to epicardial) transmural activation is apparent from recordings at electrodes A and B, positioned at adjacent ventricular sites.

preoperatively, more extensive simultaneous intraoperative mapping using an epicardial sock array are required. In addition, the persistence of preexcitation immediately after an ablative procedure would be an indication for complete epicardial mapping.

Analysis of anterograde ventricular and retrograde atrial activation patterns help to guide the surgical division of accessory pathways only if mapping is performed during arrhythmias representative of those occurring clinically, a necessity for conventional or computer mapping systems. During surgery, multiple surface electrocardiographic leads and electrograms from atrial and ventricular reference plaque electrodes are monitored continuously to confirm that electrophysiologic derangements observed intraoperatively are identical to those detected clinically. In this study, ventricular and atrial activation patterns were assessed during a single depolarization of the heart. The ventricles were mapped whenever possible during stable preexcitation and the atria mapped during stable orthodromic SVT. Although complete activation data around the AV groove were available from a single beat, a subsequent beat was routinely analyzed to assure reproducibility of the activation patterns. In 2 patients, intermittent conduction through the accessory pathway occurred intraoperatively (Fig. 3 and 4). In such instances, careful scrutiny of the QRS complex and P-wave morphologies using multiple electrocardiographic leads and comparison to preoperative findings was mandatory before concluding that these isolated beats reflected conduction through the accessory pathway and not spontaneous or mechanically induced ectopic depolarizations. In both patients, conduction through the accessory pathway, although intermittent, occurred on several occasions. In each patient, at least 2 isolated beats were analyzed before decisions regarding the surgical approach were made.

The finding of a reversal in the normal ventricular endocardial to epicardial activation pattern in instances of left free wall pathways supports the concept that these tracts insert epicardially and pass over, rather than under or through, the anular fibrosis.[13] The results of transmural mapping in these patients may have important clinical implications for improved surgical techniques. This finding, however, may not be applicable in right-sided accessory pathways because the anulus of the right ventricle is often deficient on pathologic examination.[13,14]

In conclusion, the technique of simultaneous epicardial mapping of the AV groove provides a rapid and useful means of localizing accessory pathways in patients with the WPW syndrome. Multiple-site mapping of this type may also be useful in facilitating the surgical approach to other arrhythmias, including ventricular tachycardia.

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Prospective Comparison of Holter Monitoring and Electrophysiologic Study in Patients with Coronary Artery Disease and Sustained Ventricular Tachyarrhythmias

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Baseline 24-hour Holter monitoring (HM) and electrophysiologic study (EPS) were compared in 43 consecutive patients with coronary artery disease who had sustained ventricular tachyarrhythmias to determine the fraction of patients in whom each could be performed and the fraction in whom each could be used to guide therapy. Patients were excluded from HM if sustained ventricular tachycardia (VT) requiring termination occurred and from EPS if heart failure was sufficiently severe to cause excessive risk. More patients completed EPS than HM (90% vs 71%), but this difference was not statistically significant ($p = 0.12$). Overall, HM detected arrhythmias suitable for antiarrhythmic drug assessment in 50% of patients: 30 or more ventricular premature complexes (VPCs) per hour in 50%, 10 or more VPC pairs in 44%, 5 or more runs in 19%, and 10 or more pairs and runs in 44%. Sustained monomorphic VT suitable for electropharmacologic testing was induced at EPS in 82% ($p = 0.003$ vs HM). Drug efficacy could be assessed in 70% of patients evaluated by HM, compared with 96% evaluated by EPS ($p = 0.02$). Thus, in consecutive coronary patients with sustained ventricular tachyarrhythmias, EPS could be used to guide therapy more frequently than HM.

(Am J Cardiol 1985;56:577–580)

Both electrophysiologic study (EPS) and Holter monitoring (HM) have been used to guide antiarrhythmic therapy in patients with ventricular tachyarrhythmias. The clinical value of either method depends on many factors. Previous investigators have reported the incidence of arrhythmia detection in patients referred for evaluation,[1–9] predictive value of failure to identify an arrhythmia,[4–6] probability of predicting therapy effective,[4,5,7,8] accuracy of therapy prediction,[4,5,7,10] risks[11] and cost.[12] No study has directly compared these 2 approaches to determine fraction of patients in which either could be performed or could be used to guide therapy. We performed both baseline HM and EPS in consecutive patients to address these issues.

Methods

Patients: We prospectively evaluated 33 consecutive patients with coronary artery disease admitted to a community hospital who had spontaneous ventricular fibrillation or sustained ventricular tachycardia (VT) at least 2 months after acute myocardial infarction. Myocardial infarction was diagnosed by characteristic evolutionary electrocardiographic (ECG) and enzymatic changes or pathologic Q waves in 2 or more ECG leads. All patients had at least 90% angiographic narrowing of 1 or more major coronary arteries. We excluded 1 patient who had ventricular fibrillation associated with acute aortocoronary bypass graft occlusion. Characteristics of the remaining 32 patients, all men, are summarized in Table I. Eighteen patients were admitted from the emergency ward, 12 were transferred from intensive care units within 2 days of admission and 2 were transferred from ward beds; only 2 were referred specifically for EPS.

Patients had baseline 24-hour HM after all antiarrhythmic drugs except digoxin were discontinued for 5 half-lives. EPS was performed within 24 hours of completion of HM. Patients were judged ineligible for HM to avoid multiple cardioversions if sustained, symptomatic VT requiring termination occurred during drug withdrawal or HM. In these patients, intravenous lidocaine was administered and withdrawn 8 hours before EPS. If frequent, sustained VT occurred in the baseline state and after antiarrhythmic drug administration, EPS was performed without withholding drugs for 5 half-lives. Patients were judged ineligible for EPS if they had heart failure sufficiently severe to cause excessive risk, defined as New York Heart Association functional class IV and need for continuous vasopressor support.

Holter monitoring: HM was performed with a commercial recorder (ICR 7200) using modified leads V_1 and V_5. Re-

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cordings were analyzed using a semiautomated commercial scanner (ICR 6201D). In patients who had bundle branch block or permanent pacemakers, the entire 24-hour recording was printed using a full disclosure system (ICR Variprinter) and hand counted. In the remaining patients, a QRS complex was identified as a ventricular premature complex (VPC) by a template matching system. The accuracy of the template system was verified by the scanner hourly or more often. All VPC pairs and runs of VT were hand validated. VT was defined as 3 or more consecutive ventricular complexes at a mean rate of 100 beats/min or higher. In 3 complex runs of VT, both RR intervals were required to be shorter than 600 ms. Patients were judged eligible for antiarrhythmic drug assessment if the mean VPC frequency was 30 or more per hour or the sum of VPC pairs and VT runs in 24 hours was 10 or more.

Electrophysiologic study: Quadripolar electrode catheters were inserted percutaneously and positioned in the high right atrium, right ventricular apex and His bundle recording position. An electrode catheter was positioned in the left ventricle whenever VT could not be initiated by programmed stimulation from the right ventricle. Three or 4 surface ECG leads were recorded simultaneously with intracardiac electrograms. Stimuli were 2-ms rectangular pulses delivered at 4 times diastolic capture threshold using a Bloom Associates DTU-101 stimulator and stimulus isolator. The threshold was less than 0.5 mA in all patients.

We followed a strict programmed stimulation protocol until either sustained VT was initiated or the protocol was completed. The protocol included: (1) atrial pacing up to the rate at which atrioventricular nodal Wenckebach block occurred, (2) a single extrastimulus delivered from the right ventricular apex in sinus rhythm, (3) up to 3 right ventricular apical extrastimuli in ventricular paced rhythm at 4 basic pacing cycle lengths (600, 500, 430 and 400 ms), and (4) bursts of rapid ventricular pacing to a minimum cycle length of 250 ms. If these techniques failed to initiate sustained VT, the protocol was repeated from the right ventricular outflow tract and at least 2 left ventricular sites. Patients were judged to have no inducible VT if fewer than 5 repetitive ventricular responses were initiated. Induced unsustained VT was defined as VT lasting 6 complexes to 30 seconds. Induced VT was considered monomorphic if QRS morphology was uniform and polymorphic if QRS morphology varied continuously. We considered patients eligible for antiarrhythmic drug assessment only if sustained monomorphic VT lasting longer than 30 seconds was induced.

Statistical analysis: Continuous data are presented as mean ± standard deviation. Basic comparative statistics were calculated using the chi-square test with Yates' correction or Fisher's exact test.

Results

Patient eligibility: Twenty-three patients (71%) completed HM; 9 (29%) did not complete HM, because they had sustained, symptomatic VT that required therapy during drug withdrawal (8 patients) or HM (1 patient). Symptoms of VT were syncope in 8 patients and angina associated with presyncope in 1 patient. VT was terminated by cardioversion in 8 patients and precordial thump in 1 patient. We withdrew antiarrhythmic drug treatment a second time and repeated HM in only 3 of 9 patients in whom HM could not be performed initially. All 3 completed 24 hours of control HM 1 to 3 weeks later, although 2 of them had more than 10 episodes of VT requiring cardioversion or pace termination before and after antiarrhythmic drug administration during the initial period.

TABLE I Patient Characteristics

Characteristics		
No. of pts	32	
Age (yr)	65 ± 11	
Myocardial infarction	32	
Arrhythmia		
Monomorphic VT	22	(69%)
Monomorphic VT and VF	7	(22%)
VF	3	(9%)
Cardioversion required	31	(97%)
Cardiac arrest	22	(69%)
Left ventricular function		
Left ventricular end-diastolic pressure (mm Hg)	16 ± 8	(n = 29)
Cardiac index (liters/min/m^2)	2.7 ± 0.7	(n = 29)
Left ventricular ejection fraction*	0.34 ± 0.13	(n = 32)
NYHA functional class		
I	0	(0%)
II	15	(47%)
III	12	(37%)
IV	5	(16%)

* Left ventricular ejection fraction was determined by contrast ventriculography in the 30° right anterior oblique projection in 29 patients and by radionuclide ventriculography in 3 patients.
NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

One eligible patient did not undergo EPS at the request of his referring physician; EPS was performed in 28 of the remaining 31 patients (90%). Three patients were considered ineligible for EPS because of severity of heart failure (left ventricular ejection fraction 0.14 ± 0.03, pulmonary capillary wedge pressure 25 ± 6 mm Hg, and cardiac index 1.9 ± 0.2 liters/min/m^2). At the time of EPS, antiarrhythmic drugs had been withheld for 5 half-lives (23 patients) or were present in subtherapeutic concentrations (lidocaine less than 0.3 μg/ml, 3 patients) in 26 of 28 patients (93%). Clinically significant antiarrhythmic drug plasma concentrations (lidocaine 2.6 μg/ml, procainamide 3.4 μg/ml) were measured in 2 patients at the time of EPS; both had more than 10 episodes of spontaneous, monomorphic, sustained VT in the baseline state and after drug administration. No patient had complications as a result of EPS.

Although EPS could be performed in more patients than HM, this difference was not statistically significant ($p = 0.12$). EPS was completed more frequently than HM in patients admitted through the emergency ward (15 of 17 [87%] vs 11 of 18 [61%], $p = 0.14$), but not in patients transferred from other hospitals (13 of 14 [93%] vs 12 of 14 [86%], difference not significant).

Arrhythmia detection: The prevalence of arrhythmias recorded by HM is shown in Table II. Drug assessment could be performed in 16 patients (50% of all patients, 70% of patients completing HM). Thirteen of the 18 patients (72%) in whom VT was recorded during HM had 6 or fewer episodes: 1 episode in 7 patients, 2 episodes in 2 patients, 3 episodes in 2 patients, and 4, 6, 20, 22, 34, 98 and 6,626 episodes in 1 patient each. The longest episodes were 3 complexes in 7 patients, 4 to 6 complexes in 6 patients, 7 to 10 complexes in 4 patients and 5 minutes in 1 patient. In the 16 patients with the fewest episodes, most episodes were short: 74% were 3 complexes in duration, 21% were 4 or 5 complexes, and 5% were 6 to 8 complexes. The patient who had 98 episodes had 88 episodes longer than

TABLE II Prevalence of Arrhythmias in 23 Patients Who Completed Holter Monitoring

Arrhythmia Type	Arrhythmia Frequency						
	0–1	2–9	10–29	30–99	100–299	300–999	≥1000
VPCs/hour	2	2	3	6	5	3	2
		0	1–5	6–9	10–29	30–99	≥100
VPC pairs/24 hours		3	6	2	2	1	9
VT runs/24 hours		7	10	1	2	2	1
Pairs + runs/24 hours		2	5	4	2	1	9

VPC = premature ventricular complex; VT = ventricular tachycardia.

10 complexes, the longest lasting 5 minutes; the longest episode in the patient who had 6,626 runs was 10 complexes.

Sustained monomorphic VT suitable for drug assessment was induced in 27 patients at EPS (87% of patients, 96% of eligible patients). A maximum of 13 complexes of polymorphic VT was induced in 1 patient, whose clinical arrhythmia was ventricular fibrillation. Sustained VT morphologically identical to the clinical arrhythmia was induced in both patients in whom initial EPS was performed in the presence of significant antiarrhythmic drug concentrations.

Overall, arrhythmias suitable for antiarrhythmic drug evaluation were detected more frequently by EPS than by HM: 87% vs 50% ($p = 0.003$) for all patients and 96% vs 70% ($p = 0.02$) for patients completing EPS or HM.

Discussion

Both HM and EPS have been used to guide long-term antiarrhythmic therapy in patients who have sustained ventricular tachyarrhythmias. This study prospectively determined the fraction of consecutive patients with coronary artery disease in whom each technique could be performed and used to select therapy.

HM was completed in 71% of patients and antiarrhythmic therapy was assessed in 50% (70% of evaluated patients). Ezri et al[7] recorded baseline HM in 19 patients with ventricular tachyarrhythmia, with similar results: 63% had 30 or more VPCs/hour, 58% had VPC pairs and 21% had VT.

In contrast, Graboys et al[8] reported that 100 of 106 patients (94%) with ventricular tachyarrhythmia completed baseline 48-hour HM. VPC pairs were detected in all 100 patients and VT in 90; VPC frequency was not reported. The difference in applicability of HM between our study and theirs may be a result of our higher incidence of emergency admissions (56% vs 0%); 86% of our patients who were not emergency admissions completed HM. The causes of disparity in the prevalence of recorded arrhythmias are less certain; differences in duration of monitoring[13] and patient populations may be factors.

Previous detailed analyses of HM ventricular arrhythmia complexity have been limited to ambulatory populations of apparently healthy persons,[14,15] patients with coronary disease,[16,17] and postinfarction patients.[13,17,18] As expected, the frequency and complexity of recorded arrhythmias were greater in our patients than in those populations, but the characteristics of recorded VT were similar: In ambulatory populations, 50 to 74% of 24-hour recordings that show VT had only a single episode,[19,21] 30 to 47% had only 3 complex runs,[19,20] and 16 to 55% of episodes were 3 complexes in duration.[21–23] We found that 39% had only a single episode, 39% had only 3 complex runs, and 74% of episodes in the 16 patients with fewest episodes were 3 complexes in duration.

In our study, EPS could be used to assess drug therapy more frequently than HM. Although 56% of our patients were admitted through the emergency ward and only 16% were referred specifically for EPS, the incidence and types of induced arrhythmias in our patients are similar to those reported for patients referred for EPS who had sustained VT,[1–3] ventricular fibrillation[4] or cardiac arrest.[4,5]

No programmed stimulation protocol is completely sensitive and specific. Protocols such as ours that use 3 extrastimuli have been reported to initiate clinical VT in 12 to 24% more patients than protocols using only 2 extrastimuli[2,3] as well as nonclinical polymorphic VT in up to 31% of patients without spontaneous VT.[3] To avoid false-positive outcomes, we considered only induced, sustained monomorphic VT suitable for drug assessment. Induced, polymorphic VT, which may be clinically relevant in some patients[5] and not in others,[2,3] was judged a finding of uncertain significance.

Patients who have frequent sustained VT present a particularly difficult management problem. Although suppression of spontaneous sustained arrhythmias has been used to measure drug efficacy in these patients, this approach did not distinguish spontaneous variability in arrhythmia frequency from drug effect in the 3 patients in whom we repeated baseline HM after it could not be performed initially. In contrast, EPS may be used to evaluate therapy without discontinuing antiarrhythmic drugs if the clinical arrhythmia is induced.

Our study has several limitations. We compared HM and EPS only for the fraction of patients in whom either could be used to guide therapy; we did not analyze the likelihood of predicting therapy effective, accuracy of therapy prediction, time required for therapy identification, costs, risks or institutional availability. Our population had a high proportion of acutely ill patients, and our results may not apply to a population of electively referred patients. Because HM and EPS measure different arrhythmias and the minimum arrhythmia suitable for therapy evaluation by either method is

uncertain, any comparison of these methods for arrhythmia detection must apply arbitary criteria. Our incidence of detection of arrhythmias by HM would have been lower if we had analyzed only repetitive forms. It might have been higher if we had used a longer monitoring duration[13] or continued monitoring after patients required cardioversion, although the latter approach would have limited practical, clinical application. Our incidence of induced arrhythmias suitable for EPS drug assessment might have been slightly higher if we had included polymorphic VT, but our results would have been less specific.

Both HM and EPS have specific advantages and limitations; they are neither universally applicable nor mutually exclusive. In selecting a method to evaluate antiarrhythmic therapy, our findings should be considered in conjunction with other relevant data.

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Comparative Efficacy and Safety of Oral Tocainide and Quinidine for Benign and Potentially Lethal Ventricular Arrhythmias

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The antiarrhythmic efficacy and safety of oral tocainide hydrochloride and quinidine sulfate were compared in a double-blind, 3-center, parallel trial involving 133 patients with benign and potentially lethal ventricular arrhythmias. Baseline demographic, etiologic, functional and ventricular arrhythmia data were not significantly different between the 2 groups. Two weeks of an initial placebo period were followed by 8 weeks of active drug treatment, concluding with 4 weeks of washout. Frequent 24-hour ambulatory electrocardiographic monitoring was used to judge efficacy. Ten of 27 patients (37%) receiving tocainide and 12 of 24 patients (50%) receiving quinidine had a 75% reduction with drug treatment compared with the initial placebo period ($p > 0.25$). Total abolition of ventricular tachycardia occurred in 6 of 16 patients (37%) receiving tocainide and 6 of 13 patients (43%) receiving quinidine ($p > 0.25$). Conditions that required discontinuation of therapy occurred in 18 of 67 patients (27%) receiving tocainide and 16 of 66 (24%) receiving quinidine (difference not significant). More patients had dizziness during tocainide treatment and diarrhea during quinidine treatment. Quinidine caused a prolongation in the QT interval (0.03 second); tocainide caused a slight reduction (0.01 second). No important changes in vital signs or laboratory measurements were observed in left ventricular ejection fraction when measured. Thus, tocainide, the new oral analog of lidocaine, appears to be as safe as quinidine but is slightly less effective in suppressing ventricular arrhythmias.

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Ventricular arrhythmias are important in predicting sudden cardiac death.[1] In more than 80% of patients wearing a Holter monitor sudden death was the result of a ventricular tachyarrhythmia that led to ventricular fibrillation.[2] Ventricular arrhythmias occur in 3 clinical settings, which are defined by their immediate hemodynamic consequence and their potential risk of causing sudden cardiac death[3]: benign, potentially lethal and lethal. Whether sudden cardiac death can be prevented by antiarrhythmic therapy is still an unsettled question and can be answered only by properly constituted trials.[4,5] Nevertheless, antiarrhythmic treatment for ventricular arrhythmias that are symptomatic, that cause hemodynamic sequelae or that are lethal is part of the daily practice of clinicians.

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Tocainide is a new antiarrhythmic agent with effects similar to those of lidocaine; thus, it is considered a class IB agent.[6] Tocainide increases ventricular fibrillation threshold in ischemic and nonischemic models.[7] It has little effect on electrocardiographic (ECG) intervals or myocardial hemodynamic status and its 15-hour half-life permits 2- or 3-times-daily dosing schedules. Placebo-controlled studies have shown that tocainide is effective[8] in about 50% of patients with benign and potentially lethal ventricular arrhythmias.[6] This report details the results of a multicenter clinical trial aimed at comparing the efficacy and safety of oral tocainide with those of the standard class IA antiarrhythmic agent, quinidine, in patients with benign and potentially lethal ventricular arrhythmias.[3]

Methods

Trial design: This was a 14-week, parallel, randomized, double-blind, quinidine-controlled, 3-center (Philadelphia, Rochester and Denver), outpatient study. Patients included in this trial were adults (older than 18 years) with benign or potentially lethal ventricular arrhythmias. The principal inclusion criterion was the presence of frequent ventricular premature complexes (VPCs), averaging at least 60 per hour over 48 hours of ambulatory monitoring during 2 weeks of

TABLE I Comparison of the Baseline Characteristics of the Two Drug Groups

	Tocainide (n = 67)	Quinidine (n = 66)
Mean age (yr) and range	59 (28–83)	58 (20–86)
Men	54	54
NYHA class		
I	36	35
II	23	19
III	8	10
IV	0	1
Unknown	0	1
ASHD	39	36
CHF	12	5
HTN	5	8
MVP	1	1
Idiopathic	16	16
Use of digoxin	9	9
Median VPCs/hour	293	279
Mean VPCs/hour	438 ± 422	506 ± 519

ASH = atherosclerotic heart disease; CHF = congestive heart failure; HTN = hypertension; MVP = mitral valve prolapse; NYHA = New York Heart Association; VPCs = ventricular premature complexes.

placebo therapy. All antiarrhythmic drugs, including β blockers (but excluding digitalis preparations), were discontinued before the initial 2-week placebo period. Patient exclusion criteria included known allergy to quinidine or amide-type local anesthetic agents, myasthenia gravis, use of a cardiac pacemaker, a creatinine level above 2.5 mg/dl, the presence of second- or third-degree atrioventricular (AV) block, trifascicular block, right bundle branch block with left posterior hemiblock, a prolonged QT interval syndrome or Wolff-Parkinson-White syndrome.

After signing the informed consent form, which had been approved by the local Institutional Review Boards, the patients began a 2-week baseline period during which 2 placebo tablets were taken orally every 6 hours. Eligible patients were assigned to 1 of 2 treatment groups according to an allocation schedule of random numbers. Patients received either 600 mg of tocainide hydrochloride every 12 hours or 300 mg of quinidine sulfate every 6 hours for the 8 weeks of active treatment. Participants were required to take 2 kinds of tablets (tocainide or its placebo and quinidine or its placebo) to maintain the double-blind design of the trial. Then, patients entered a 4 week post–active drug treatment period, when placebo was again administered as 2 tablets every 6 hours. During the initial placebo period each patient underwent a complete medical history, weekly physical examination, a 12-lead electrocardiogram, ophthalmologic examination, chest radiograph and complete clinical laboratory screening. Patients were also evaluated at weeks 3, 4, 6, 8 and 10 during the active drug period and as well as weeks 12 and 14 during the final

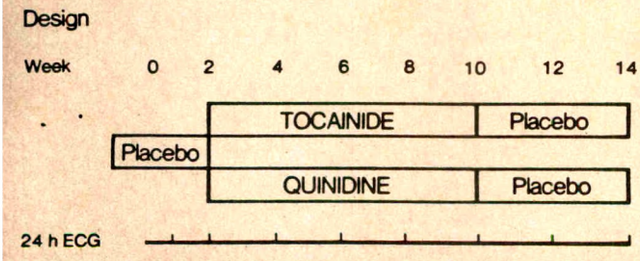

FIGURE 1. The placebo-controlled, parallel study design using tocainide, 600 mg twice daily, and quinidine, 300 mg 4 times daily. Twenty-four-hour Holter recordings (ECG) were recorded as shown.

placebo. On each of these 9 occasions, vital signs were recorded, a history was taken and physical examination was performed. Ophthalmalogic and chest radiographic examinations were repeated during the placebo period after treatment. Clinical laboratory screening was obtained during weeks 1, 4, 10 and 12 and a 24-hour continuous Holter monitoring recording was performed during weeks 1, 2, 4, 6, 8, 10, 12 and 14 (Fig. 1).

In the Denver center, 13 patients were subjected to a noninvasive determination of left ventricular ejection fraction using a dynamic gated radionuclide angiographic technique. This test was performed during the placebo periods before and after treatment and at the end of 6 weeks of active drug therapy.

Data analysis: For the cardiovascular and quantitative laboratory parameters, within-group test of changes from before treatment were performed by combining the Wilcoxon signed rank statistics for each investigator. To assess interaction between investigator and treatment and of investigator main effects, an analysis of variance on the overall relative ranks was performed. Between group tests of treatment effects were performed using a nonparametric (rank) randomized block analysis on ranks within each block (investigator). When there was a significant between-group difference before treatment and it appeared that the difference might affect the analysis of changes from before treatment, an analysis of covariance was performed on the actual values using the baseline value as the covariate. Qualitative laboratory parameters and adverse effects were analyzed using Fisher's exact test on 2 × 2 tables. The significance level for the test of interaction was 0.10; all other tests used the 0.05 significance level.

The efficacy of tocainide and quinidine was evaluted by comparing the VPC frequency on the available 24-hour Holter recordings during the active drug period with the average of the two 24-hour Holter recordings during the initial 2-week placebo period. A 75% reduction in VPC frequency was considered to be an effective response. The number of responders per treatment group was compared using Fisher's exact test on 2 × 2 tables.

A central research facility (the Cardio Data Systems of United Medical Corp., Haddonfield, New Jersey) was used to analyze all of the 24-hour recordings from the 3 centers. Analysts were blinded as to the treatment of the patient. Details of the nature of the system as well as its quality control features, validity, reproducibility and precision have been reported.[9]

Results

Patient characteristics: The 3 centers enrolled a total of 136 patients. Three of these 136 patients never received active drug treatment, 26 were discontinued from the study because of inadequate VPC frequency during the pretreatment baseline period, 34 were discontinued before completing the trial because of adverse reactions (1 during the final placebo period) and 2 were discontinued for administrative reasons. Table I is a list of the baseline characteristics for the 67 patients who randomized to tocainide and to the 66 patients randomized to quinidine. There were no significant differences between the 2 drug groups for any of the categories listed.

Suppression of ventricular arrhythmias: When patients are considered who met the inclusion baseline VPC frequency (at least 60 per hour) criteria and when patients who were withdrawn because of adverse reactions or administrative reasons are considered as

TABLE II Degrees of Suppression of Ventricular Premature Complexes in the Two Drug Groups

		VPC Suppression (%)				
	n	<49	50–74	75–84	85–99	100
Tocainide	27	13	4	4	4	2
Quinidine	24	7	5	1	9	2

VPC = ventricular premature complex.

treatment failures, then 101 patients are analyzable for the determination of suppression of ventricular arrhythmias. A 75% reduction on active drug treatment compared to the pretreatment placebo period was found in 12 of 54 patients (22%) randomized to tocainide and 18 of 47 (38%) randomized to quinidine ($p = 0.086$). Figure 2 details the mean suppression of VPCs during the 3 phases of the protocol in patients randomized to quinidine or tocainide. For patients with ventricular tachycardia in the pretreatment period, complete abolition of ventricular tachycardia was seen in 8 of 38 patients (21%) randomized to tocainide and 10 of 28 (36%) randomized to quinidine ($p > 0.25$).

When patients with inadequate VPCs at baseline patients who discontinued for administrative or adverse reactions and, those who did not have a return of VPCs on the Holter monitor obtained in the final placebo period are excluded, then 51 patients are available for efficacy analysis. A 75% reduction in VPCs was observed in 10 of 27 patients (37%) randomized to tocainide and 12 of 24 (50%) randomized to quinidine ($p > 0.25$). Complete abolition of ventricular tachycardia occurred in 6 of 16 patients (37%) randomized to tocainide and 6 of 13 (43%) randomized to quinidine ($p > 0.25$). Table II is a list of the percent reduction using several different categories in comparing patients treated with tocainide or quinidine for VPCs.

Adverse reactions: Thirty-four of 67 patients (51%) receiving tocainide and 42 of 66 (64%) receiving quinidine reported adverse effects (difference not significant [NS]). Reactions requiring discontinuation from the protocol occurred in 18 of 67 patients (27%) receiving tocainide and 16 of 66 (24%) receiving quinidine (NS). Table III is a list of reasons for withdrawal in the 2 treatment groups. There were significant differences between the treatment groups in the prevalence of dizziness and diarrhea (Fig. 3).

TABLE III Adverse Reactions

Reason for Withdrawal	Tocainide (n = 67)	Quinidine (n = 66)
CNS (ataxia, tremor, dizzy)	8	0
Rash	4	5
CNS and gastrointestinal	3	4
Gastrointestinal (diarrhea, nausea, vomiting and anorexia)	1	3
Congestive heart failure	1	1
Death	1	1
Intercurrent viral infection	0	1
Atrial fibrillation and VT	0	1*
Total	18 (27%)	16 (24%)

* Occurred in post drug placebo period.
CNS = central nervous system; VT = ventricular tachycardia.

Proarrhythmia electrocardiogram and other laboratory parameters: Two patients died, one in each group, on the 21st day of therapy. Neither death was considered to be related to the active drug by the treating investigator. In this trial, no patient had greater than a 3-fold increase in VPC frequency during active therapy compared with control and no patient had sustained ventricular tachycardia during active drug treatment.

PR and QRS intervals did not change significantly during active drug treatment compared to baseline in either the tocainide or quinidine group. There was a significant increase in the QT interval during therapy with quinidine (a mean increase of 0.03 second) com-

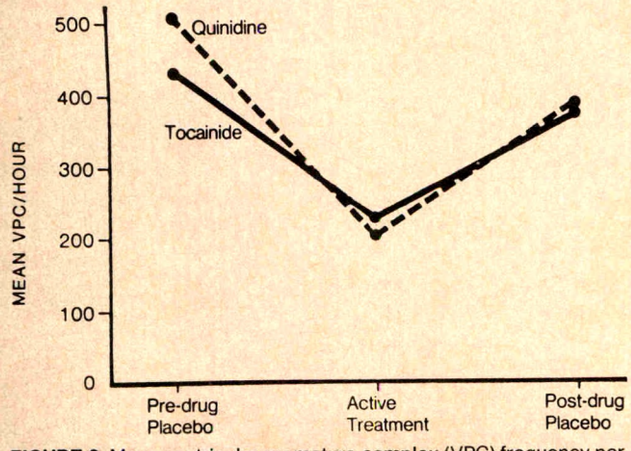

FIGURE 2. Mean ventricular premature complex (VPC) frequency per hour from Holter monitoring data for patients randomized to quinidine and tocainide. Predrug placebo, active treatment and the postdrug placebo periods are compared.

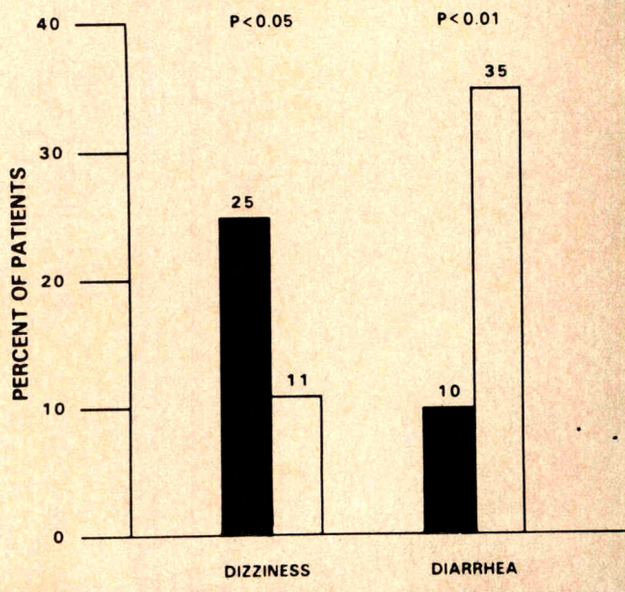

FIGURE 3. The percent of patients experiencing the adverse reactions of either dizziness or diarrhea with tocainide (**solid bars**) and quinidine (**open bars**) treatment (n = 133).

pared with the QT interval in patients receiving tocainide, which either did not change or decreased 0.01 second at week 6 on therapy ($p < 0.01$).

No clinically significant changes occurred in vital signs or laboratory tests nor were there any significant changes on comparing the chest radiographic and ophthalmologic evaluations before and after treatment.

Left ventricular function: In the Denver center, 13 patients (7 receiving tocainide and 6 receiving quinidine) were studied by radionuclide angiography. After 6 weeks of treatment the mean left ventricular ejection fraction decreased slightly, by 26% from the initial placebo baseline mean of 35.6% ($p < 0.05$). The mean ejection fraction returned toward the initial baseline value after the 4-week posttreatment placebo period, but remained lower than baseline (mean 34.0%). No significant difference was detected between the 2 placebo periods. The mean left ventricular ejection fraction in the quinidine-treated group decreased slightly, by 0.12%, from an initial baseline mean of 38.5%. At the end of the posttreatment placebo treatment the ejection fraction decreased further, to a mean of 36.0%, which was significantly lower than that during the initial baseline period ($p < 0.01$). No significant differences were detected between treatment groups during the placebo and active drug periods. There was no significant reduction in clinical hemodynamic stability in any of the patients evaluated.

Discussion

This double-blind, parallel, 3-center study compared the efficacy and safety of oral tocainide, 600 mg every 12 hours, with quinidine sulfate, 300 mg every 6 hours, in patients with benign and potentially lethal ventricular arrhythmias. The results indicate that these 2 agents *at the doses used* are comparable in terms of safety, although quinidine is slightly more effective than tocainide.

Quinidine was chosen as the comparison agent because it is one of the most commonly used antiarrhythmic agents available in the United States and frequently serves as a standard comparative agent.[9–12] In this study, 38 to 50% of patients responded at the 75% level of VPC reduction, depending on the criteria used for patient inclusion for analysis. A range of 50 to 75% of patients responding to quinidine therapy has been shown in other studies[9–11] using doses of quinidine sulfate up to 400 mg every 6 hours. Twenty-two to 37% of patients receiving tocainide achieved a 75% VPC reduction. A total of 10 short-term placebo controlled tocainide trials in 99 patients have been performed using tocainide, with doses of 200 to 800 mg every 8 hours to 400 to 1,000 mg every 12 hours. Approximately 51% of patients have shown a more than 75% suppression in VPC frequency.[3] Tocainide has also been shown to be effective in the suppression of ventricular ectopy in postinfarction patients and during long-term treatment.[13,14] Three trials have been reported that compared the effectiveness of tocainide to that of procainamide, with no significant differences being demonstrated in effectiveness or safety. Each of these 3 studies has methodologic limitations.[15–17] A limitation of the efficacy data in this study is that multiple doses of quinidine and tocainide were not compared, thus eliminating the evaluation of a true dose-response comparison of these 2 agents. However, the doses of tocainide and of quinidine were considered to be the usual effective clinical dose in which side effects are mild or minimized.

Approximately one-fourth of the patients receiving both tocainide and quinidine discontinued treatment because of adverse reactions. The most frequent reason for discontinuation in the tocainide group was related to its central nervous system effects in which ataxia, tremor and dizziness were primarily manifested. Conversely, the gastrointestinal side effects predominated in patients receiving quinidine and diarrhea but also nausea, vomiting and anorexia were often seen. These percentages of side effects are quite similar to those reported in other studies.[9,10,16,18]

As could be predicted from the electrophysiologic effects, quinidine caused a prolongation of the QT interval by lengthening the JT segment, whereas tocainide had either no effect or caused a slight reduction. No significant changes were seen in the PR or QRS intervals in this study. No patient had a proarrhythmic response. The lack of QT interval prolongation by tocainide may imply that the potential for induction of a serious ventricular proarrhythmic event may be less common with tocainide than with other classes of antiarrhythmic agents.[19]

No significant changes in vital signs, laboratory variables or important hemodynamic changes were induced by either quinidine or tocainide. No patient had symptoms of congestive heart failure with either drug.

Tocainide to lidocaine are similar in their electrophysiologic and hemodynamic effects. Often, one can predict the response to tocainide by the response to lidocaine.[6] Also important is the fact that tocainide has no important interactions with β blockers, digoxin or coumadin.[6] Thus, this study has also shown that the efficacy and safety of tocainide compare favorably to quinidine, and tocainide is only slightly less effective. Tocainide's advantages of not prolonging the QT interval, of having no important negative inotropic or proarrhythmic effects, and of being useful even with a twice-daily dosage schedule, which promotes compliance suggest, that tocainide will be a useful addition to the antiarrhythmic armamentarium.

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Incidence of Proarrhythmic Effects from Quinidine in the Outpatient Treatment of Benign or Potentially Lethal Ventricular Arrhythmias

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To determine the prevalence and importance of proarrhythmic events secondary to the initiation of quinidine therapy in outpatients with benign or potentially lethal ventricular arrhythmias, the data from 360 patients treated with quinidine as part of 3 outpatient drug trials were retrospectively reviewed. These patients had at least 30 ventricular premature complexes per hour during placebo treatment and had no evidence of unstable clinical states, hypokalemia, digitalis toxicity, atrial fibrillation or a prolonged QT interval (longer than 0.50 second). The quinidine dose varied from 200 to 400 mg 4 times a day for 2 to 4 weeks. Proarrhythmic effect was defined on Holter monitoring as a 400% increase in frequency of ventricular premature complexes, the presence of new ventricular tachycardia not previously identified or a 10-fold increase in the number of beats of ventricular tachycardia. There was no difference in the demography, response to quinidine therapy or side effects on quinidine among the 3 trials. Six of 360 patients (2%) had a proarrhythmic response and none of these patients had hemodynamic symptoms, required hospitalization or died from the proarrhythmic event. Thus, quinidine can be safely initiated to outpatients who meet the inclusion criteria cited herein.

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Although antiarrhythmic drugs have been used for several decades, only recently has their full potential to aggravate or induce ventricular arrhythmias (the so-called proarrhythmic effect) been appreciated.[1,2] However, the prevalence of proarrhythmic events resulting from antiarrhythmic drug treatment is different in patients with benign and potentially lethal ventricular arrhythmias[1,3] from those with lethal ventricular arrhythmias. Benign ventricular arrhythmias are those that occur in patients with no structural heart disease, do not produce hemodynamic consequences, and have a very low risk of associated sudden cardiac death. Lethal ventricular arrhythmias cause immediate hemodynamic consequences (such as syncope and symptomatic hypotension) and are associated with the highest rate of sudden cardiac death. Patients with lethal ventricular arrhythmias usually have markedly depressed left ventricular function and severe structural heart disease. Patients with potentially lethal ventricular arrhythmias have structural heart disease or compromised left ventricular function such that the presence of ventricular arrhythmias is associated with an increased risk of sudden death. These arrhythmias, however, do not cause hemodynamic symptoms and the only indication for their treatment is the hope that their suppression will prevent sudden cardiac death. Antiarrhythmic treatment of patients with lethal ventricular

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TABLE I Demographic Characteristics of the Three Trials

	A	B	C
Pts receiving quinidine	139	154	67
Mean age (yr)	58	60	59
Men	69%	71%	69%
CAD	52%	51%	47%
VPCs/24 hours at baseline (Mean ± SD)	429 ± 423	451 ± 466	417 ± 413

CAD = coronary artery disease; SD = standard deviation; VPC = ventricular premature complexes.

arrhythmias is properly initiated in hospital using monitoring facilities and careful drug dosing. Although there is increasing concern regarding proarrhythmic effects, the actual frequency of these events during outpatient initiation of antiarrhythmic therapy is uncertain. Therefore, many physicians have also resorted to hospitalizing patients with benign or potentially lethal arrhythmias before initiating drug therapy to control ventricular arrhythmias. Because of the impact of new prospective reimbursement schedules and the high cost associated with continuous electrocardiographic (ECG) monitoring in hospital, we retrospectively reviewed 3 large antiarrhythmic drug trials to determine the prevalence and importance of proarrhythmic events secondary to the initiation of quinidine in outpatients with benign or potentially lethal ventricular arrhythmias.

Methods

The data from 3 clinical drug trials in which patient entry criteria were identical (patients had to have either benign or potentially lethal ventricular arrhythmias without a history of lethal ventricular arrhythmias) were pooled. All patients had a minimum average of 30 ventricular premature complexes (VPCs) per hour on at least two 24-hour Holter monitors during placebo treatment at least 1 week after discontinuation of all prior antiarrhythmic agents. In all 3 trials patients were excluded if they had evidence of prior allergy or severe side effects to quinidine, or had hypokalemia, digitalis toxicity, atrial fibrillation, or second- or third-degree atrioventricular block. No patient had a myocardial infarction within 6 weeks of entry or uncontrolled noncardiac disease or uncompensated congestive heart failure (New York Heart Association class III or IV). Patients with a QT interval that was longer than 0.50 second were also excluded.

Ambulatory electrocardiographic monitoring in all 3 trials was analyzed by the same independent research analysis service (Cardio Data, Inc., United Medical Corp., Haddonfield, NJ). All patients had at least 1 Holter recording at least 18 hours in duration while receiving quinidine.

One trial was a 16-center, parallel, double-blind, placebo-controlled trial of flecainide acetate vs quinidine sulfate in 342 outpatients.[4] In this trial, 139 patients were placed on quinidine therapy after 1 week of placebo treatment. Two 24-hour Holter recordings established entry criteria. Quinidine was then prescribed initially at a dose of 300 mg 4 times daily for 2 weeks followed by 400 mg 4 times daily if an 80% reduction in VPC frequency was not seen during treatment with the lower dose.

The second trial was a 9-center, crossover, double-blind, placebo-controlled trial of encainide hydrochloride vs quinidine sulfate in 187 patients. One hundred fifty-four patients received quinidine. (Some patients were discontinued after initial randomization to encainide before quinidine therapy.)

TABLE II Efficacy and Safety of Quinidine in the Three Trials

	A	B	C
Pts responding			
VPCs	55%	67%	53%
VT	66%	78%	41%
Side effects			
Any	65%	74%	41%
% D/C	15%	25%	27%

D/C = discontinued from study because of side effects; VPCs = ventricular premature complexes; VT = ventricular tachycardia.

After 1 week of placebo and two 24-hour Holter recordings, patients initially received 200 and then 400 mg of quinidine sulfate 4 times daily each for 1 week. The larger dose was used only if at least a 75% reduction in VPC frequency was not seen on the lower dose.

The third study was a 1-center, parallel, single-blind, controlled trial comparing 4 types of quinidine in 67 patients. After 1 week of washout during placebo therapy and two 24-hour Holter recordings to establish entry criteria, patients were randomized in a parallel fashion to 4 types of quinidine, each for 3 weeks, with three 24-hour Holter recordings obtained during this time. Quinidine sulfate, using either 1,200 mg of Quinora® (Eli Lilly) or the extended preparations Quinidex® (AH Robins) or Quiniday® (AH Robins) were prescribed or quinidine gluconate (Quinaglute Dura Tabs®, Berlex Laboratories) at a dose of 1,296 mg/day.

The definition of proarrhythmic effect (on Holter monitoring) used in this trial was adopted from that of Velebit et al,[5] who required at least a 400% increase in VPC frequency with quinidine treatment compared to baseline; the presence of new ventricular tachycardia (VT) not previously identified or a 10-fold increase in the number of beats of VT during quinidine treatment compared to the baseline.

Results

The demographic information comparing all 3 clinical trials indicate that there were no statistically significant differences in the age, gender, proportion with coronary artery disease, or ventricular arrhythmia frequency at baseline (Table I).

The percent of patients responding with at least 75% reduction in VPC frequency compared with control in these trials as well as a 75% reduction in beats of VT are shown in Table II. Again, there was no statistically significant difference between the 3 trials in the efficacy of quinidine to control VPCs or VT. Table II also details the prevalence of side effects reported during the trial and the percent of patients requiring premature discontinuation during the trial because of an adverse effect to quinidine. Again, no statistically significant differences were seen between the 3 trials.

The proarrhythmic responses in these 3 trials based on the criteria noted above are described in Table III. The prevalence of a proarrhythmic effect observed was 2%; no patient had hemodynamic symptoms, required hospitalization or died from a proarrhythmic event. Three patients in the flecainide-quinidine trial died,[4] but all 3 deaths were documented to be the result of acute myocardial infarction. Four patients in the encainide-quinidine trial had QT intervals longer than 0.55 second during quinidine treatment, but no patient was observed to have this effect in the other 2 trials.

Discussion

The occurrence of a proarrhythmic effect induced by antiarrhythmic therapy is particularly important in patients with benign or potentially lethal ventricular arrhythmias, because reduction of VPCs in these patients has not been determined to result in prevention of sudden death. If antiarrhythmic agents are used in these patients special cautions are necessary to be certain of their safety and efficacy. A follow-up Holter recording is mandatory after initiating antiarrhythmic therapy to be certain that the proarrhythmic effect is absent and that the agent is effective.[1,3]

In this report we evaluated the safety of initiating quinidine to outpatients as antiarrhythmic treatment. The data clearly document that in patients with benign or potentially lethal ventricular arrhythmias in a stable clinical state and without hypokalemia or atrial fibrillation, quinidine therapy is safe to initiate in the outpatient setting, because the rate of a proarrhythmic effect was only 2% and no patient had a serious hemodynamic adverse reaction or sudden death or required hospitalization. Quinidine was chosen as the reference agent because it is the most commonly used antiarrhythmic agent in the United States.[4]

The 3 trials reviewed were comparable even though they were performed at different times. All 3 used the same central laboratories for data analysis, similar dosing schedules and duration of therapy, and they were comparable in demographic and clinical factors between the patient groups. In addition, the efficacy and side effect rates in these trials during quinidine therapy were comparable. Therefore, the ability to examine these 3 study groups as a homogeneous population to define the prevalence of proarrhythmia appears to be valid. The results of these trials and the safety of outpatient initiation of quinidine are relevant to patients only with benign or potentially lethal ventricular arrhythmias and without hypokalemia, digitalis toxicity and atrial fibrillation. Patients with more severe left ventricular dysfunction, especially if associated with these abnormalities, and patients with lethal ventricular arrhythmias were not studied herein, and these patients have had a higher prevalence and severity of proarrhythmic effects than the patients reported in this study.[1] Until the proarrhythmic prevalence and severity are determined in such patients, they should have quinidine initiated in hospital under ECG monitoring.

TABLE III Proarrhythmic Response in the Three Trials

	A (n = 139)	B (n = 154)	C (n = 67)
VPC 400% inc.	2	2	0
New VT	0	0	0
VT 1,000% inc.	0	0	2
QT >0.55	0	4	0
Deaths	3 (All MI)	0	0
Proarrhythmic effect = 6/360 (2%)			

Inc. = increase; MI = myocardial infarction; VPC = ventricular premature complexes; VT = ventricular tachycardia.

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Ambulatory Electrocardiographic Recordings at the Time of Fatal Cardiac Arrest

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The relation between arrhythmias at cardiac arrest and the outcome of arrest is poorly understood. The Holter monitor tracings of 13 patients were reviewed after they sustained an in-hospital cardiac arrest during ambulatory electrocardiographic monitoring. All had a prior cardiac arrest or cardiac syncope. Twelve patients had ventricular tachycardia (VT) as their initial arrest arrhythmia and 1 patient had bradycardia followed by ventricular fibrillation (VF). VT degenerated to VF in 10 of 12 patients after a mean interval of 96 ± 31 seconds (± standard error of the mean). The number of VT runs increased significantly during the hour immediately preceding arrest ($p = 0.004$). Despite prompt resuscitation efforts in 12 patients, only 6 survived. The 6 survivors and 6 nonsurvivors were not different with regard to age, ejection fraction, extent of coronary artery narrowing and time to first defibrillation. However, degeneration to VF within 30 seconds of arrest (5 of 6 nonsurvivors and 1 of 6 survivors, $p = 0.04$) and a slower rate of VT at the onset of arrest (166 beats/min in nonsurvivors and 227 beats/min in survivors, $p = 0.02$) were associated with unsuccessful resuscitation.

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Despite the high prevalence of sudden cardiac death, few patients have had a cardiac arrest while wearing an ambulatory electrocardiographic (Holter) recorder such that the initiating cardiac arrhythmia and the period immediately before this arrhythmia can be accurately described. The Cardiac Arrhythmia Clinic at The Johns Hopkins Hospital serves as a referral center for the evaluation and treatment of ventricular tachycardia (VT) and ventricular fibrillation (VF). During the past 3 years, 13 patients have had an in-hospital cardiac arrest while wearing a Holter recorder. All patients were ambulatory on an inpatient ward and had not suffered a recent myocardial infarction. When we reviewed these continuous electrocardiographic (ECG) tracings, we wanted to find answers to 3 questions. First, is there an increase in the number of runs of VT in the hours before a cardiac arrest? Second, is VT rather than VF the initial arrhythmia at the time of cardiovascular collapse? Third, are there clinical, angiographic or arrest arrhythmia findings that correlate with successful resuscitation?

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Methods

Patient selection: All patients in this retrospective study met 4 entry criteria: (1) each had a history of prior cardiac arrest or syncope and were admitted to hospital for evaluation and treatment; (2) all had an ambulatory ECG recorder in place during cardiac arrest and cardiopulmonary resuscitation and defibrillation were performed on all patients; (3) no patient had sustained an acute myocardial infarction during the 10 days before the cardiac arrest; and (4) there was no evidence of any new myocardial injury that might be responsible for the cardiac arrest. Except for 1 patient, all were undergoing telemetric monitoring such that the arrest was immediately recognized and resuscitation promptly started.

Ten of 13 patients underwent coronary arteriography (9 patients) or postmortem examination (1 patient), which allowed definition of the underlying structural heart disease. For patients with coronary heart disease, the extent of disease was assessed by the number of coronary arteries or major branches narrowed at least 70% in diameter. Left ventricular ejection fraction was determined in each patient by contrast angiography or gated cardiac blood pool scan.

Ambulatory electrocardiographic analysis: Delmar 445B 2-channel ambulatory ECG recorders (Delmar Avionics)

were used. Tapes were scanned by a Trendsetter electrocardioscanner analysis system. Quantitative counts of VT runs and the arrest sequence were checked by visual inspection of the tracings.

VT was present when at least 3 ventricular ectopic complexes occurred at a rate of at least 120 beats/min. VF was present when the ventricular wave pattern became disorganized and grossly irregular (Fig. 1 and 2). R-on-T phenomenon was defined as an ectopic ventricular complex with a prematurity index (R-R′/QT) of 1 or less.

The ambulatory ECG recording was separated into 4 periods for analysis: (1) the arrest sequence, (2) the hour immediately preceding arrest, (3) the 6-hour interval from 7 hours to 1 hour before the arrest, and (4) any recording more than 7 hours before the arrest. The arrest sequence was examined to determine how often an R-on-T ventricular premature beat was the initiating beat of the arrest arrhythmia, the nature of the initial arrhythmia at the beginning of the arrest, the rate and duration of the initial arrhythmia, whether it changed to another arrhythmia and the elapsed time from initial arrest arrhythmia to the first defibrillation. Finally, we noted whether sinus rhythm was reestablished and if the patient survived resuscitation.

In analyzing the time before arrest, the number of runs of VT during each of the 3 periods before the arrest was determined. The heart rate of the last 3 beats immediately before the arrest was calculated. A corrected QT interval for the complexes immediately before arrest was calculated for each patient using the Bazzett equation[1,2]: $QTc = QT/\sqrt{R\text{-}R'}$. For this study, a corrected QT interval longer than 0.42 second for men and longer than 0.43 for women was considered prolonged.

Statistical methods: Continuous data are reported as mean values ± standard error of the mean. Differences between the means of independent observations were assessed by an unpaired Student t test. Analysis of survival after arrest was by Fisher's exact test. Analysis of the increase in VT in the hours before arrest was by a nonparametric t test. Significance was established at a value <0.05.

Results

Clinical findings: The mean age of the patient group was 55 ± 4 years (range 22 to 83). Before admission to the hospital, 8 patients had a history of cardiac arrest and 5 patients had a syncopal episode considered secondary to a ventricular tachyarrhythmia. Ten of the 13 patients had had congestive heart failure that had been successfully treated by medications. Two of the 13 patients had a prior unmonitored in-hospital arrest. Ten patients had coronary artery disease and all 10 had survived at least 1 acute myocardial infarction. At coronary arteriography, 2 patients had 1-vessel coronary disease, 1 patient had 2-vessel disease and 4 patients had 3-vessel disease. Two patients had idiopathic dilated cardiomyopathy. One patient had no recognizable structural heart disease. Three patients with prior infarction did not undergo arteriography but were presumed to have coronary disease. The mean ejection fraction for the entire group was 23 ± 5% (range 7 to 67%).

The antiarrhythmic medications being used at the time of the recorded cardiac arrest were: procainamide (2 patients), procainamide and lidocaine (1 patient), aprindine (2 patients), flecainide (4 patients) and amiodarone (1 patient); 3 patients were not receiving antiarrhythmic medication. All medication was started after admission to hospital. No patient was receiving vasopressors or other medications that could have enhanced the appearance of a cardiac arrhythmia. Seven patients were taking digitalis, but none had serum levels above the therapeutic range. Serum potassium levels were normal in all patients. No patient complained of chest pain before arrest and none of the survivors of the arrest had ECG or cardiac enzyme evidence of myocardial injury.

Arrhythmia at time of cardiac arrest: VT was the initial arrhythmia at time of cardiac arrest in 12 patients. One patient had bradycardia followed by immediate VF. Examples of the arrhythmias are shown in Figures 1 and 2. No patient had ventricular asystole as the initial arrest arrhythmia. The initial VT rate was 203

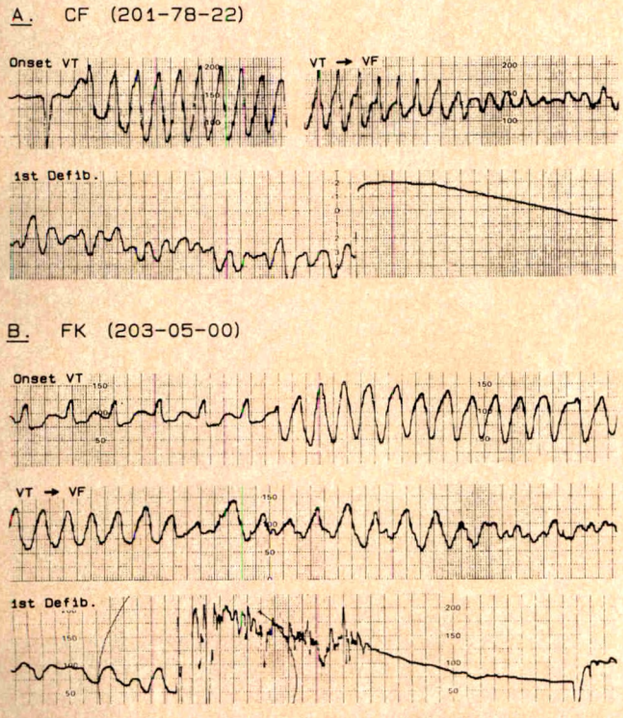

FIGURE 1. Cardiac arrest arrhythmia as recorded by a Holter monitor. Onset ventricular tachycardia (VT), conversion VT to ventricular fibrillation (VF) and first defibrillation for patients CF (**A**) and FK (**B**).

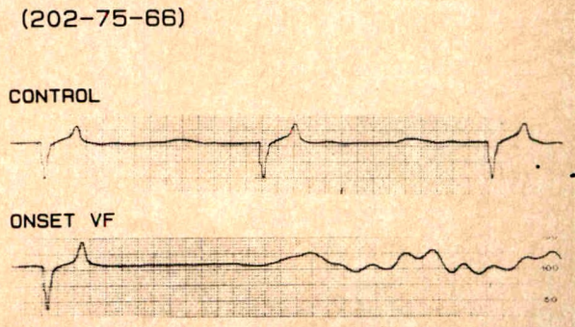

FIGURE 2. Cardiac arrest arrhythmias as recorded by a Holter monitor. Onset of ventricular fibrillation (VF) at the instant of cardiac arrest for patient JS.

TABLE I Electrocardiographic Findings at Cardiac Arrest

Pt	VT Runs/Hour Before Arrest			Heart Rate (beats/min) Before Arrest			
	Period 1 (>7 hr)	Period 2 (7 → 1 hr)	Period 3 (1 → 0 hr)	Period 3	Last 3 Beats	Initial VT Rate	Max VT Rate
WC	1	1	4	125	120	240	240
JJ	0.2	0	35	61	70	120	120
FK	0.5	0	16	76	80	180	180
BD	0	0	0	100	70	250	280
JP	0	0	1	89	120	180	240
JW	0.3	0.3	1	77	120	207	240
CF	1	25	147	63	50	210	270
FS	79	3	66	110	110	120	120
MR	0	2	31	68	100	200	200
JS	NR	0	0	110	36	VF	VF
ST	NR	0.3	4	68	120	280	300
JH	NR	0.2	2	90	60	240	330
RE	NR	NR	8	60	40	210	240

All values are mean values.
NR = no recording; VF = ventricular fibrillation; VT = ventricular tachycardia.

± 15 beats/min (range 120 to 280). The maximal VT rate was 232 ± 20 beats/min (range 120 to 330) (difference not significant) (Table I). VT degenerated to VF in 10 of the 12 patients when the initial arrhythmia was VT. The mean duration of VT before degeneration to a grossly disorganized rhythm considered to be VF for these 10 patients was 96 ± 31 seconds (range 5 to 300) (Fig. 3). Two patients had VT throughout the arrest. In no instance did VF spontaneously convert to VT.

Electrocardiographic recording before arrest: The number of VT runs per hour in the 3 periods before cardiac arrest is shown in Table I. Two patients had no VT before their arrest. Ten of 11 patients with VT before arrest had more VT runs in the hour immediately preceding the arrest ($p = 0.004$). For this analysis, periods 1 and 2 were compared with period 3. No patient had a decrease in the number of VT runs in the hour before arrest.

Ten of 13 patients had R-on-T phenomenon during the hours before arrest, but only 2 patients had it as the initiating beat of the arrest arrhythmia. Seven patients had a prolonged QTc interval. Of these patients, 2 were receiving flecainide (QTc = 0.43 and 0.46), 2 were receiving aprindine (QTc = 0.54 and 0.67), 1 patient was receiving procainamide (QTc = 0.56) and 2 were receiving no antiarrhythmic medications (QTc = 0.56 and 0.53).

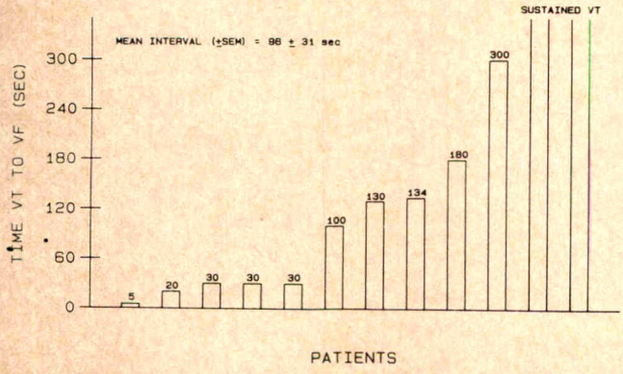

FIGURE 3. Conversion of ventricular tachycardia (VT) to ventricular fibrillation (VF) during cardiac arrest. Interval between onset of arrest VT and conversion of VT to VF is shown for each patient (JS excluded). SEM = standard error of the mean.

Outcome after cardiac arrest: Analysis of outcome after cardiac arrest was limited to the 12 patients undergoing telemetric monitoring who received prompt resuscitation. Six of these 12 patients survived and 6 did not. Several factors were examined to determine whether any clinical, anatomic or electrocardiographic findings were associated with a successful resuscitation (Table II). Survivors and nonsurvivors were examined with respect to the conduct of the resuscitation. There was no apparent difference in the drugs given, the presence of a palpable pulse, effectiveness of sternal compression, attempt at right ventricular overdrive pacing or endotracheal intubation. There was no difference in the interval from cardiovascular collapse to the first attempted defibrillation (Table II). Although survivors had a better ejection fraction (29%) than nonsurvivors (17%), the difference was not significant. There was no difference in the extent of coronary disease.

One difference between survivors and nonsurvivors was the duration of VT during the arrest before it degenerated to VF. In 5 of 6 nonsurvivors, VT deteriorated to VF in less than 30 seconds or VF was the initial arrest arrhythmia. In 5 of 6 survivors, progression of VT to VF was either delayed by more than 30 seconds or VT persisted and was the only arrhythmia during the arrest. This difference in the duration of VT between survivors and nonsurvivors was significant ($p = 0.04$) (Table II). A second and surprising difference was the initial rate of VT. Nonsurvivors had a slower initial rate of VT than survivors (Table II). The patient with immediate bradycardia and VF was not included in this analysis.

Discussion

Most information concerning arrhythmias during cardiac arrest is based on either studies of infarct patients monitored in a coronary care unit[3] or the first rhythm recorded by a life-support team at an out-of-hospital arrest.[4–6] Such studies are primarily biased toward periinfarctional arrhythmias and the findings

TABLE II Factors Influencing Resuscitation After Cardiac Arrest

Pt	Age (yr)	Multivessel Disease (70%)	EF (%)	QTc (sec)	Digoxin	Initial VT Rate (beats/min)	VT → VF in ≤30 sec	Time to 1st Defib (sec)
				Survivors				
WC	62	+	38	0.29	0	240	0	60
RE	22	0	16	0.36	+	210	0	480
BD	57	0	15	0.39	+	250	+	210
JW	37	0	67	0.56	0	207	0	280
JP	61	+	29	0.56	+	180	0	260
ST	51	0	13	0.53	+	280	0	270
Mean ± SEM	48 ± 6	2/6	29 ± 3	0.44 ± 0.04	4/6	227 ± 14	1/6	260 ± 22
				Nonsurvivors				
JJ	54	+	15	0.43	+	120	+	240
FK	63	+	13	0.46	+	180	+	460
JS	56	−	19	0.41	0	VF	+	180
CF	68	−	14	0.54	0	210	0	310
FS	67	+	38	0.67	0	120	+	60
MR	36	0	7	0.37	+	200	+	240
Mean ± SEM	57 ± 5	3/4	17 ± 2	0.48 ± 0.04	3/6	166 ± 19	5/6	248 ± 20
p value	NS	NS	0.08, NS	NS	NS	0.02	0.04	NS

EF = ejection fraction; NS = not significant; SEM = standard error of the mean; VF = ventricular fibrillation; VT = ventricular tachycardia.

may not be representative of patients with recurrent sudden death and no infarction.

Arrhythmias at time of cardiac arrest: VT initiated the arrest sequence in 12 of 13 patients (92%) and then degenerated to VF in 10 (83%) of these 12. This appears to be the most common sequence of arrhythmias during cardiac arrest. Sixty-three cases of cardiac arrest occurring during 24-hour ambulatory ECG recording have been reported previously[7–10]; in 47 (74%) VT was the initial arrest arrhythmia and in 9 (14%) it was VF, 6 patients (9%) had profound bradycardia and 1 patient (2%) had asystole. Of the 47 patients with VT, in 37 (78%) the rhythm degenerated to VF.

Three reasons may explain the discrepancy between the high prevalence of VT as the initial arrest arrhythmia in our series and the findings of others that VF was the first recorded arrhythmia at out-of-hospital arrests.[4–6] First, there is an inherent delay between cardiovascular collapse outside hospital and arrival of a life-support team when an ECG rhythm strip can be recorded. In our study VT rapidly deteriorated to VF (mean 96 seconds). Thus, many patients with out-of-hospital arrest found in VF probably had VT as their first arrhythmia. Second, VF is the most common initial arrhythmia at the time of cardiac arrest during acute myocardial infarction.[3,11] Approximately 50% of out-of-hospital cardiac arrest patients are subsequently found to have new myocardial injury.[4,12,13] No patient in our report had chest pain before their arrest and none of the 6 survivors had ECG or cardiac enzyme changes to suggest new myocardial injury at the time of arrest. Third, the antiarrhythmic therapy that 10 of our 13 patients were receiving may be responsible for a higher proportion of patients having VT instead of VF as the initial arrest arrhythmia.

Increasing ventricular tachycardia during the hour before arrest: We confirm the findings of others that a significant increase in the frequency of VT runs occurs in the hours preceding a cardiac arrest. Pratt et al[7] (15 patients reported) and Lewis et al[8] (12 patients reported) both noted a significant increase in the frequency of VT runs in the 3 hours before arrest. Nevertheless, it should be noted that 11 of 40 patients (27%) in these 3 studies had no VT during the 3 monitored hours before arrest. Any arrhythmia detection device designed to warn against an impending arrest would not have identified these patients by an increase in the number of VT runs. Also, it is not known how often a substantial increase in VT runs occurs but is not followed by cardiac arrest.

Failure to resuscitate: We are concerned why resuscitation efforts were not more successful in our patient series despite prompt assistance and defibrillation. No previous study has examined whether clinical, angiographic and electrocardiographic variables are associated with successful resuscitation of patients who have had a cardiac arrest. Weaver et al[14] reported the follow-up of 64 patients who had coronary angiography soon after resuscitation from out-of-hospital arrest. They found that the ejection fraction of 14 patients who later died suddenly or had another episode of VF was significantly lower than that of those who had no further arrhythmic event (39% vs 51%). We did not find a correlation between left ventricular dysfunction and successful resuscitation, nor did we find a higher proportion of patients with multivessel disease among nonsurvivors. The duration of VT was different between survivors and nonsurvivors. Progression from VT to VF in less than 30 seconds was associated with an unsuccessful resuscitation effort. Conversely, if VT persisted or there was a delay of more than 30 seconds before VT degenerated to VF, patients had a greater chance of successful resuscitation. Rapid degeneration to VF may reflect a greater degree of electrical disorganization that is more difficult to correct.

Clinical significance: Because these patients had been referred to our hospital after a prior out-of-hospital cardiac arrest or syncope, our presumption is that the in-hospital arrhythmic findings would be similar to those found at the time of an out-of-hospital cardiac

arrest if ambulatory ECG recordings had been available. Because VT and VF are the 2 arrhythmias most often found at the time of a cardiac arrest, recognition of both arrhythmias is necessary for any detection or defibrillation device. An implantable device that recognizes both arrhythmias has been successfully used.[15] Pacemaker capability appears less important because profound bradycardia or asystole as the probable mechanism of cardiac arrest occurs in less than 10% of patients.

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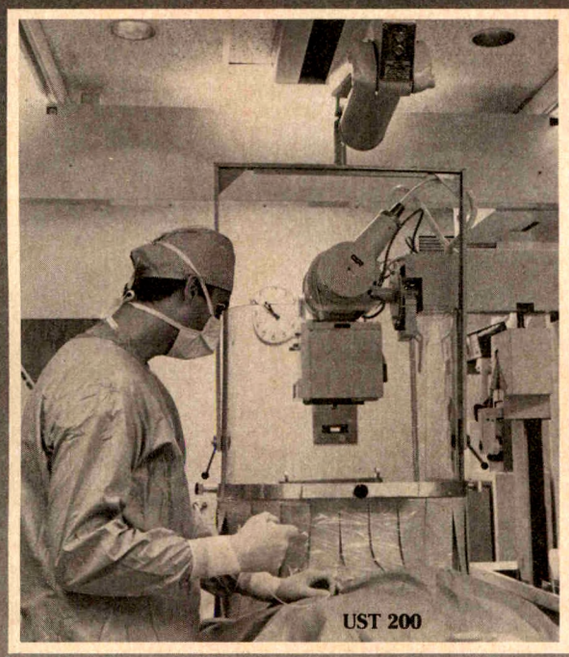
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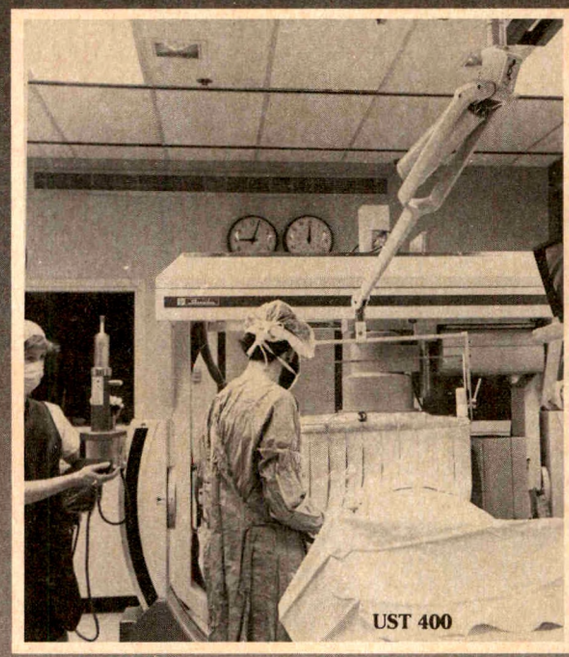
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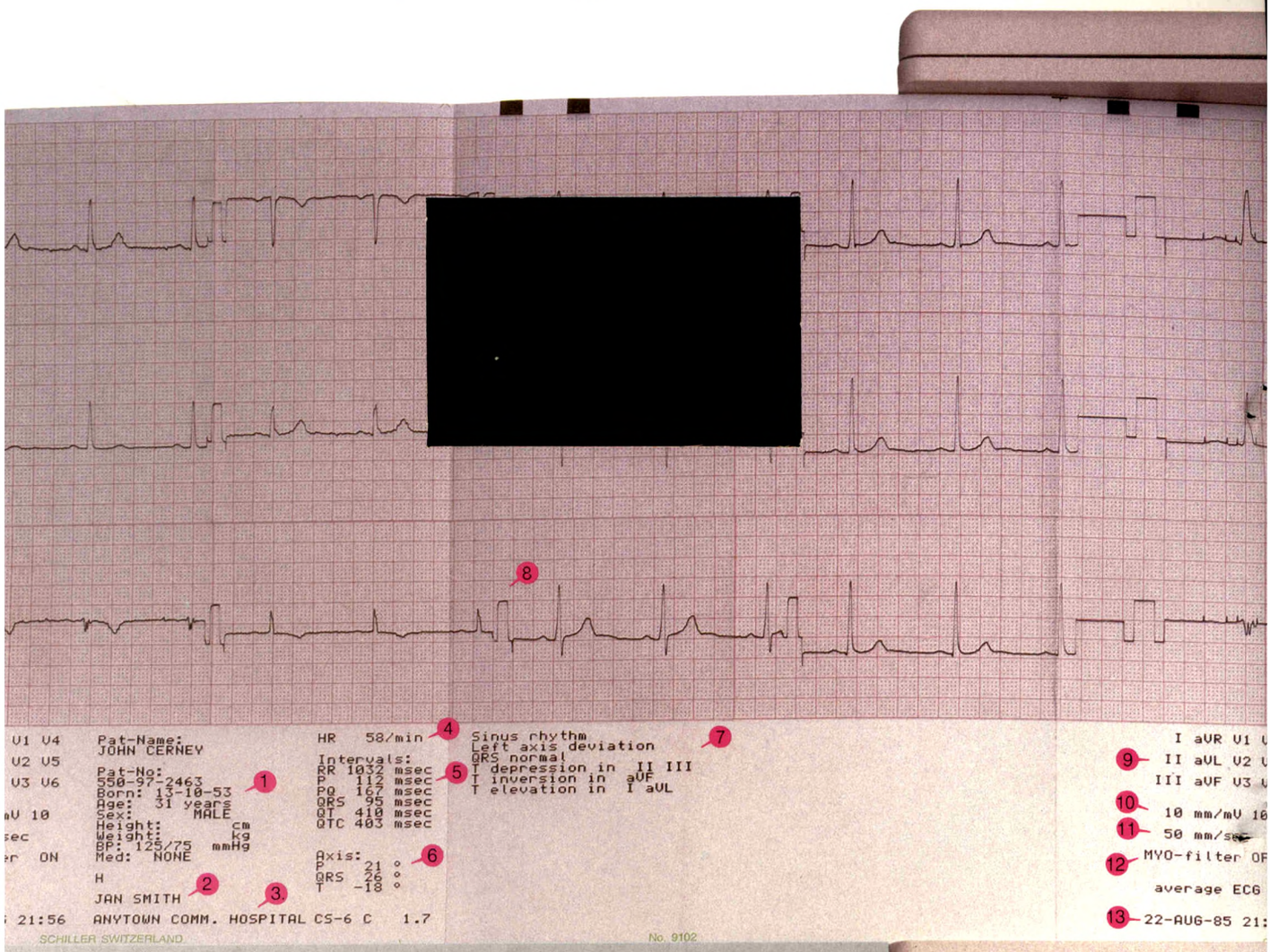

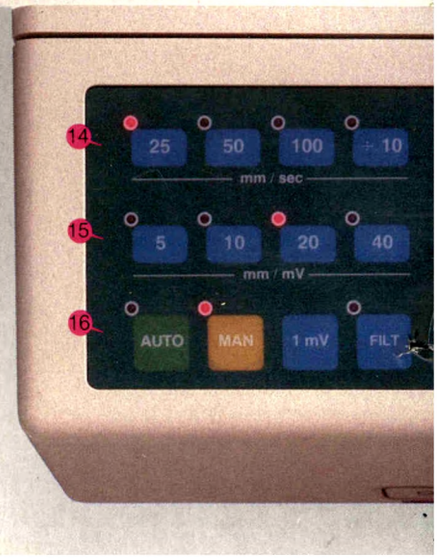

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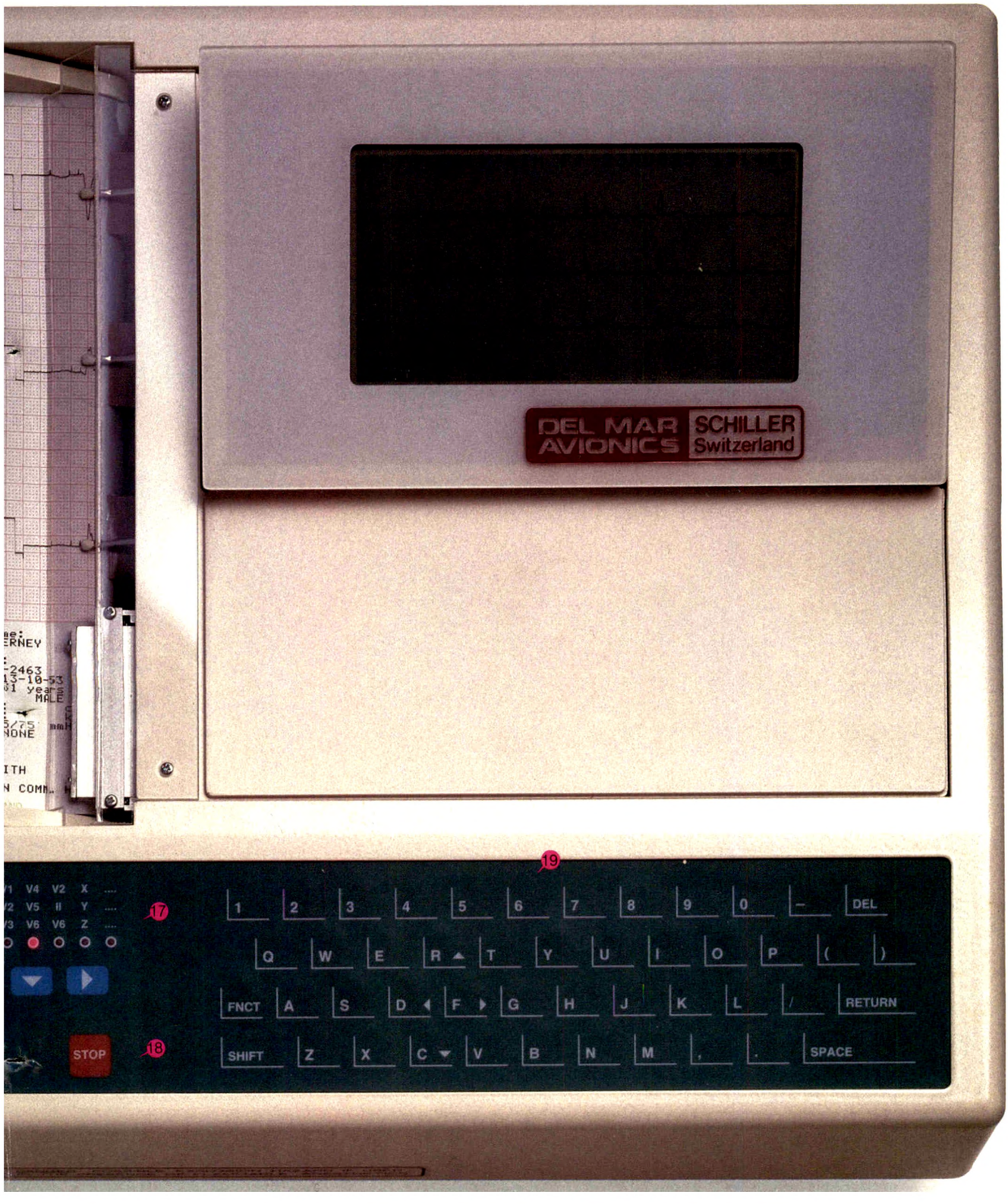

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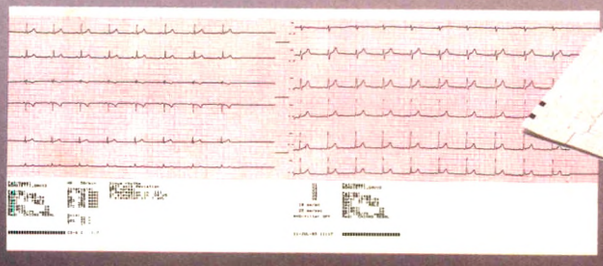

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Usefulness of Programmed Stimulation in Predicting Efficacy of Propafenone in Long-Term Antiarrhythmic Therapy for Paroxysmal Supraventricular Tachycardia

MATTHIAS MANZ, MD, GERHARD STEINBECK, MD, and BERNDT LÜDERITZ, MD

The electrophysiologic effects of intravenous (i.v.) and oral propafenone were evaluated in 14 patients with Wolff-Parkinson-White syndrome and in 10 patients with atrioventricular (AV) nodal reentrant tachycardia. The effective refractory periods of the right atrium and the AV node increased after both preparations. In patients with Wolff-Parkinson-White syndrome, i.v. propafenone blocked anterograde accessory pathway conduction in 2 patients and retrograde conduction in 1; during oral therapy, accessory pathway conduction block occurred in 2 additional patients. The mean cycle length of the supraventricular tachycardia (SVT) increased from 338 ± 60 ms to 387 ± 56 ms ($p < 0.05$) after i.v. application, and from 336 ± 65 ms to 367 ± 65 ms ($p < 0.05$) during oral propafenone. The shortest pacing interval maintaining a 1:1 AV conduction increased from 325 ± 65 ms to 368 ± 81 ms ($p < 0.05$) after i.v. infusion, and from 333 ± 57 ms to 369 ± 75 ms ($p < 0.05$) during oral therapy. There was no difference in the electrophysiologic effects between i.v. and oral propafenone. The induction of SVT was prevented by i.v. propafenone in 10 of 20 patients and in 4 additional patients with oral propafenone. During follow-up, 6 of 7 patients, whose SVT could not be initiated by electrophysiologic drug testing, remained free from recurrences, whereas 5 of 7 patients with inducible tachycardia had recurrences of SVT. Thus, in patients with SVT, propafenone prolonged accessory pathway and AV nodal conduction and had a beneficial effect on circus movement tachycardia. Electrophysiologic drug testing with propafenone predicts its efficacy during chronic therapy in most patients.

(Am J Cardiol 1985;56:593–597)

Propafenone hydrochloride decreases the maximal rate of increase of the action potential, and shortens the action potential duration in atrial and ventricular structures of the heart; therefore, it belongs to the class I antiarrhythmic agents.[1–3] Previous studies showed that propafenone is effective for control of supraventricular and ventricular arrhythmias.[4–7] Electrophysiologic investigations for the evaluation of propafenone in patients with supraventricular tachycardia (SVT) are limited[8–12]; only a few patients have been studied during oral therapy.[9,11] The present study evaluates the influence of propafenone on the electrophysiologic properties in patients with Wolff-Parkinson-White (WPW) syndrome and with atrioventricular (AV) nodal reentrant tachycardia after intravenous (i.v.) application; it also determines whether acute electrophysiologic drug testing can predict the efficacy of propafenone during oral therapy in patients with SVT.

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Methods

Patients: In 24 patients (8 women and 16 men, aged 12 to 70 years), diagnostic investigations were performed. The patients were studied in the nonsedated state and did not receive cardioactive drugs for at least 48 hours before the investigation. Each patient gave an informed written consent. All patients had 8 ± 6 episodes (range 2 to 24) of sustained SVT in the 12 months before entrance into the study. Previous antiarrhythmic therapy included 2.5 ± 1 antiarrhythmic agents (range 1 to 4) in 22 cases; 2 patients had no previous antiarrhythmic treatment.

Electrode catheters were inserted through the right femoral and left basilic vein, and were placed into the right atrium, right ventricle, coronary sinus and just below the tricuspid valve to record the His bundle activity. Electrocardiographic leads I, II and V_1 and 3 bipolar intracardiac leads were recorded simultaneously. Atrial and ventricular stimulation were performed using the single-test stimulus method as well as regular pacing at increasing rates. Effective refractory pe-

TABLE I Effect of Propafenone on Effective Refractory Periods of the Anomalous Pathway

Pt	Sex & Age (yr)	Anterograde Conduction			Retrograde Conduction		
		Control	1 mg/kg i.v.	450–600 mg/day p.o.	Control	1 mg/kg i.v.	450–600 mg/day p.o.
1	F12	310	290	—	230	≤230	—
2	M46	290	290	—	240	280	—
3	M43	310	≤310	—	≤250	≤260	—
4	M47	290	Block	—	—	—	—
5	M40	Concealed conduction			290	290	—
6	F41	Concealed conduction			290	390	Block
7	M50	340	390	340	360	530	380
8	M40	Concealed conduction			250	≤240	≤250
9	M20	Concealed conduction			≤250	≤240	≤240
10	M20	260	Block	—	Block	Block	—
11	M62	280	290	Block	360	Block	Block
12	M19	270	270	280	230	≤270	≤240
13	M18	260	270	270	270	≤280	300
14	M24	310	320	340	≤260	≤260	≤280

— = not given or not determined.

riods of the accessory pathway and of the AV node were both obtained with a basic stimulation rate of 100/min using the single-test stimulus method. The mean cycle length during reentrant tachycardia and the shortest atrial interval during incremental atrial pacing were compared with the results after drug treatment.[12] The following criteria for diagnosis of AV nodal reentrant tachycardia were used: (1) induction of SVT related to a critical AH delay with both incremental pacing and atrial extrastimulus testing; (2) demonstration of anterograde dual AV nodal pathway; (3) atrial activation occurring before or simultaneously with the onset of ventricular activation during SVT; and (4) normal retrograde atrial activation sequences during SVT. Retrograde anomalous pathway conduction during SVT was proved by the following criteria: (1) abnormal retrograde atrial activation sequence; and (2) ability to capture the atria during SVT with critically timed ventricular extrastimuli when the His bundle was refractory.[13–15]

After the initial electrophysiologic study, 1 mg/kg of propafenone was administered intravenously over 5 to 10 minutes. After a 5-minute period of drug distribution, the electrophysiologic protocol was repeated. In 14 patients, who underwent a second electrophysiologic study, the stimulation protocol was repeated after 5 to 7 days of oral therapy with 150 mg of propafenone 3 to 4 times daily; 1 patient received 150 mg 5 times daily. The study was performed 1 to 2 hours after the last dose was administered. Seventeen patients continued receiving oral therapy with propafenone and were followed on an out patient basis at 4- to 8-months intervals.

Group data are presented as mean ± standard deviation of the mean. Friedman's analysis of variance by ranks and Wilcoxon matched-pairs signed-ranks test were used.

Results

Patterns of WPW syndrome were present in 14 patients, including 4 patients with concealed anterograde accessory pathway conduction. The electrophysiologic study revealed a right-sided accessory pathway in 2 patients, a left-sided pathway in 7 and a septal pathway in 4 (no localization in 1 patient). AV nodal reentrant tachycardia could be demonstrated in the remaining 10 patients.

Atrial and ventricular refractory periods: The effective refractory periods of the right atrium increased from 210 ± 24 ms to 225 ± 29 ms ($p < 0.05$) after i.v. application, and from 212 ± 23 ms to 228 ± 41 ms during oral therapy ($p < 0.05$). The effective refractory periods of the right ventricle were unaffected by propafenone (i.v.: control 236 ± 20 ms, propafenone 236 ± 22; oral: control 239 ± 21 ms, propafenone 246 ± 22 ms).

Accessory pathway properties: The influence of propafenone on the effective refractory period of the accessory pathway is listed in Table I. After i.v. propafenone, anterograde conduction of the accessory pathway was blocked in 2 patients, and retrograde conduction in 1 patient. During oral therapy, 2 additional patients had a block of accessory pathway conduction, 1 in the anterograde and 1 in the retrograde direction. The anterograde effective refractory periods of the remaining patients increased in 4, remained unchanged in 3 and decreased in 1 patient. Retrograde effective refractory periods were determined by the refractoriness of the ventricle in 8 patients; therefore, accessory pathway effective refractory periods could not be measured in these cases. In the remaining patients, prolongation of the effective refractory periods was found. The shortest atrial intervals with 1:1 AV conduction during incremental atrial pacing are given in Figure 1. After i.v. administration of propafenone, the intervals increased from 325 ± 65 ms to 368 ± 81 ms ($p < 0.05$). During oral therapy, an increase from 333 ± 57 ms to 369 ± 75 ms was observed ($p < 0.05$).

Atrioventricular node: Table II is a summary of the effects of propafenone on the effective refractory periods of the AV node for both anterograde and retrograde conduction. There was an increase in the effective refractory periods after i.v. and oral propafenone in most patients. Retrograde conduction of patient 4 was blocked after i.v. and oral propafenone.

Reentrant tachycardia: Intravenous propafenone increased the mean cycle length of the induced reentrant tachycardia from 338 ± 60 ms to 387 ± 56 ms ($p < 0.05$). A similar increase of the mean cycle length from 336 ± 65 ms to 367 ± 65 ms was noted during oral drug treatment ($p < 0.05$, Fig. 2). Induction of reentrant

TABLE II Effect of Propafenone on Effective Refractory Periods of the Atrioventricular Node

Pt	Sex & Age (yr)	Anterograde Conduction			Retrograde Conduction		
		Control	1 mg/kg i.v.	450–600 mg/day p.o.	Control	1 mg/kg i.v.	450–600 mg/day p.o.
1	F12	≤220	≤220	—	—	—	—
6	F41	≤230	≤240	230	—	—	—
7	M50	270	300	230	—	—	—
8	M40	250	240	280	—	—	—
9	M20	370	390	410	—	—	—
14	M24	260	280	290	310	330	320
15	M18	320	350	—	220	260	—
16	F47	220	260	—	285	360	—
17	M58	≤275	—	—	450	—	—
18	F51	270	—	—	450	—	—
18	F51	270	—	270	≤250	≤260	≤270
19	M41	270	300	300	≤280	300	380
20	F70	≤300	≤340	—	—	—	—
21	F60	250	290	370	≤280	≤270	≤270
22	F51	280	270	260	≤250	510	—
23	F46	≤210	250	290	≤250	≤260	290
24	M23	260	280	290	340	Block	Block

— = not given or not determined.

tachycardias could be estimated in 20 patients during control and after infusion of propafenone. Two patients had only paroxysmal atrial fibrillation; no tachycardia could be initiated in 1 patient and persistence of atrial fibrillation terminated the study in 1 other patient. Intravenous administration of propafenone prevented induction of reentrant tachycardias in 10 patients. The echo zone of induction was unchanged in 7 patients, smaller (>20 ms) in 2 and wider (>20 ms) in 1. During oral therapy, the inducibility of the reentrant tachycardia returned in 1 patient (Fig. 3). On the other hand, the induction of sustained reentrant tachycardia was no longer possible in 4 other patients during oral therapy; in 2 of these 4 patients, 5-beat runs of nonsustained tachycardia were recorded.

Patient follow-up: After discharge from the hospital, 17 patients continued oral therapy with 557 ± 70 mg of propafenone. Three of these patients left the study: 1 patient was referred for cardiac operation because of pulmonary stenosis together with corrected transposition of the great arteries, and died within 1 month; 1 died of bronchial cancer after 4 months without SVT recurrence; and 1 was lost to follow up because he re-

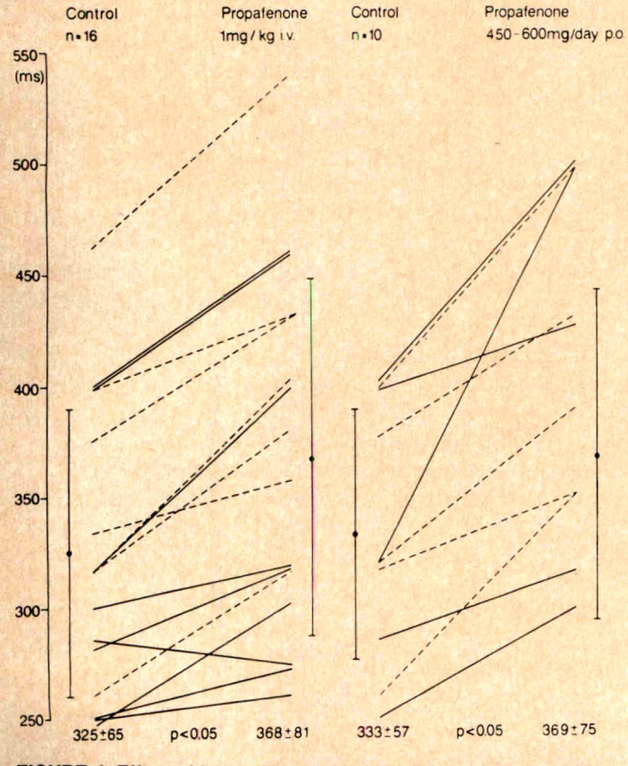

FIGURE 1. Effect of intravenous (i.v.) and oral (p.o.) propafenone on the shortest atrial intervals with 1:1 atrioventricular conduction during atrial incremental pacing in patients with Wolff-Parkinson-White syndrome (**solid line**) and atrioventricular reentrant tachycardia (**broken line**).

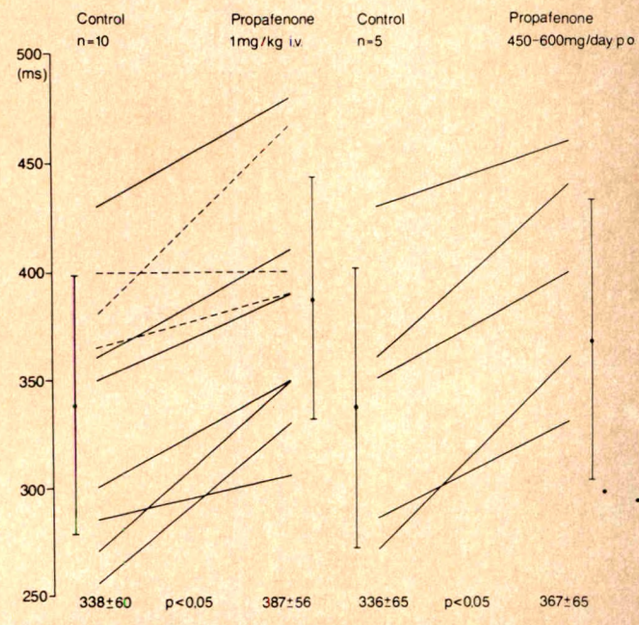

FIGURE 2. Effect of intravenous (i.v.) and oral (p.o.) propafenone on the mean cycle length of induced supraventricular reentrant tachycardia in patients with Wolff-Parkinson-White syndrome (**solid line**) and atrioventricular nodal reentrant tachycardia (**broken line**).

turned to his native country. Of the remaining patients, 2 were treated with amiodarone because of recurrent atrial fibrillation, 3 received β-blocker therapy and 2 had no long-term antiarrhythmic therapy because they had a low incidence of SVT (2 in 12 months). Among the 14 patients who were treated during long-term patient management with propafenone, SVT in 7 patients (group 1) was controlled during electrophysiologic drug testing (both i.v. and oral treatment in 6 patients and oral treatment alone in 1 patient). In group 1, 6 of 7 patients remained free from recurrences for a mean of 25 ± 7 months. One patient reported 3 self-terminating SVTs in 30 months (control: 15 SVTs in 12 months) and continued to take the substance. Two patients in group 1 interrupted drug treatment for 2 and 3 months, experienced recurrences and started to take propafenone again. In group 2 patients, whose SVT was not controlled by i.v. (n = 5) and oral (n = 2) propafenone treatment during the electrophysiologic study, 5 had recurrences of SVT during a period of 18 ± 11 months. Two of these patients had only 1 and 2 recurrences per year and continued to take the drug. Three of the remaining patients had more frequent episodes of SVT (3 in 4 months, 5 and 7 within 12 months); these patients were treated with amiodarone. The incidence of SVT for the 2 groups was the same before entry into the study. The follow-up of group 2 was shorter because therapy in 3 patients was switched to amiodarone. Four patients complained about gastrointestinal side effects at the beginning of the oral therapy, but no patient had to discontinue propafenone.

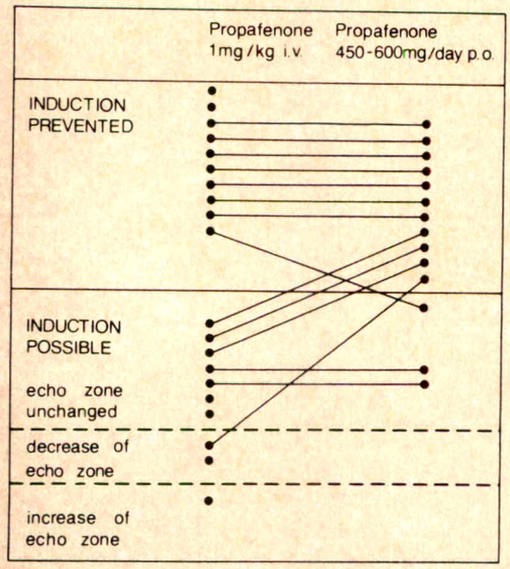

FIGURE 3. Inducibility of supraventricular reentrant tachycardia after intravenous (i.v.) and oral (p.o.) treatment with propafenone in 20 patients. Intravenous propafenone prevented the induction of the reentrant tachycardia in 10 patients (6 with atrioventricular [AV] nodal reentrant tachycardias, 4 with Wolff-Parkinson-White [WPW] syndrome). The electrophysiologic study could be repeated in 14 patients during oral therapy; in this cohort, reentrant tachycardias of 7 patients (5 with AV nodal reentrant tachycardias, 2 with WPW syndromes) were not inducible as before. In 4 additional patients (1 with AV nodal reentrant tachycardia, 3 with WPW syndromes), the tachycardia could not be initiated any longer; however, tachycardia returned in 1 patient with WPW syndrome.

Discussion

In our investigation, propafenone had a uniform effect on the refractoriness of the atrium, the AV node and accessory pathway in anterograde and retrograde direction. These results are in accordance with previous studies,[8–12] which reported a higher percentage of anterograde accessory pathway block, probably a result of the 1.5- and 2 mg/kg-dose of propafenone given. The prolongation of the refractory periods and the slowing of conduction resulted in a decrease of the heart rate during SVT and protected against rapid ventricular rates during atrial fibrillation.

The effect of i.v. propafenone on the refractory periods was of the same magnitude as the effect during oral treatment. With respect to the induction of SVT, some patients appeared to benefit additionally during oral drug trials. The slightly better results during oral treatment compared with i.v. application might have been caused by active metabolites such as 5-hydroxypropafenone.[17] In a previous study, the effects of i.v. and oral treatment with propafenone was demonstrated in a cohort of 5 patients.[9]

In the present study, patients with complete suppression of SVT at the electrophysiologic drug trial appeared to have less recurrences of SVT during long-term therapy. Effective prophylactic drug therapy could be predicted in most patients with WPW syndrome[18] or AV nodal reentrant tachycardia by serial electrophysiologic drug testing.[19] Recently Klein et al[20] reported that acute drug testing with verapamil could predict the response to long-term therapy with oral verapamil. These data support the assumption that the electrophysiologic drug trial can predict the efficacy of long-term therapy in most patients with SVT.

Limitations: The result of the electrophysiologic study may be influenced by the tone of the autonomous nervous system at the different days of the study. The electrophysiologic investigation could be repeated only in 14 patients and chronic propafenone therapy was continued only in two-thirds, resulting in patient selection. Tachycardiac attacks were assessed by the reports of the patients, but objective recordings were lacking.

Clinical implications: Propafenone had a uniform effect on AV node structures and on accessory pathway tracts, resulting in a decrease of the rate during reentrant tachycardias and during the atrial tachyarrhythmias. Propafenone proved an effective antiarrhythmic agent for long-term treatment of patients with SVT. Acute drug testing with propafenone can predict its effects during chronic therapy in most patients with SVT.

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Effects of Atenolol on Exercise Capacity in Patients with Mitral Stenosis with Sinus Rhythm

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Exercise capacity is frequently impaired in patients with mitral stenosis (MS) and sinus rhythm (SR). The resulting increased heart rate, which shortens the diastolic filling period, and the increased cardiac output lead to further elevations of left atrial pressure and subsequent pulmonary congestion. The effect of the β-receptor blocking agent atenolol, 100 mg/day, was assessed in 13 patients with MS and SR. Exercise performance was assessed using a modified multistage Bruce protocol after 2 weeks of placebo and after 2 weeks therapy with atenolol in a single-blind, crossover, placebo-controlled, randomized study. Atenolol resulted in significant decreases in mean heart rates at rest and during exercise ($p = 0.0015$) and a significant increase in total exercise time ($p = 0.0015$). Maximal exercise capacity was also significantly improved ($p = 0.0015$). All patients were both objectively and subjectively improved by atenolol. Thus, β-blockade with atenolol improves exercise capacity in patients with MS and SR and may be of benefit to most such patients. The improved effort tolerance is attributed to reduction of the exercise-associated sinus tachycardia by β-blockade, allowing a longer diastolic filling period and better left atrial decompression. (Am J Cardiol 1985;56:598–601)

Exercise capacity is frequently impaired in patients with mitral stenosis (MS). The pressure gradient across the mital valve is directly related to the diastolic blood flow through the orifice and inversely related to the orifice size and duration of the diastolic filling period.[1–3] Any increase in cardiac output or decrease of the diastolic filling period, as occurs with tachycardia, produces an exponential rise in the pressure gradient.[3] The result is reflected clinically by dyspnea on exertion and, in severe cases, by the precipitation of pulmonary edema.

Intravenous administration of propranolol has been studied by catheterization and has a beneficial effect on hemodynamic values at rest[3–8] and during supine exercise.[6,7] D'Annunzio and Mobilij[8] showed hemodynamic improvement at rest after oral propranolol administration for 1 month in 5 patients with MS and sinus rhythm (SR). We found only 1 study that compared exercise capacity both before and after the chronic administration of β-blocking agents.[9] We studied 13 patients who had significant MS and were in SR. These patients were evaluated in a single-blind, placebo-controlled, crossover study. The β blocker selected for the study was the cardioselective agent atenolol.

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Methods

Patients: Thirteen consecutive patients with isolated MS and SR were subjected to a prospective crossover, single-blind, placebo-controlled study. There were 11 female and 2 male patients, aged 15 to 35 years. All were in functional class II or III of the New York Heart Association classification. The diagnosis of MS was made clinically and confirmed by echocardiography in every patient. MS was considered significant in all 13 patients as judged by the echocardiographic finding of a mitral valve orifice area of less than 1.5 cm. All patients received oral diuretic therapy throughout the study period. All had evidence of pulmonary arterial hypertension, as judged by a palpable right ventricular impulse and a loud pulmonic component of the second heart sound. Chest roentgenographic and electrocardiographic findings were all compatible with the clinical diagnosis.

Study protocol: The 13 patients were subjected to a 2-phase, crossover study with each phase consisting of 2 weeks. Seven patients began with placebo and the other 6 with oral atenolol treatments, 100 mg taken in the morning. A β-blocker

TABLE I Measurements During Atenolol and Placebo Phases

	Placebo	Atenolol	p Value
Rest heart rate (beats/min)	(13) 88 ± 12	(13) 58 ± 8	0.0015
Exercise heart rate (beats/min)			
Stage I	(13) 115 ± 16	(13) 81 ± 15	0.0015
Stage II	(13) 127 ± 17	(13) 93 ± 16	0.0015
Stage III	(9) 146 ± 11	(13) 106 ± 15	0.0077
Stage IV	(3) 164 ± 10	(9) 119 ± 12	0.0015
Stage V		(4) 140 ± 10	
Blood pressure (mm Hg)			
Rest			
Systolic	106 ± 12	101 ± 10	NS
Diastolic	71 ± 10	70 ± 7	NS
Stage I			
Systolic	111 ± 16	105 ± 16	NS
Diastolic	66 ± 10	66 ± 11	NS
Stage II			
Systolic	110 ± 16	110 ± 15	NS
Diastolic	63 ± 11	62 ± 16	NS
Stage III			
Systolic	117 ± 19	101 ± 14	NS
Diastolic	60 ± 16	57 ± 18	NS
Stage IV			
Systolic	107 ± 15	99 ± 7	
Diastolic	53 ± 6	50 ± 12	
Stage V			
Systolic		97 ± 21	
Diastolic		42 ± 15	
Exercise time (min)	9 ± 2	11 ± 2	0.0015
Maximal exercise capacity (units)	45 ± 29	84 ± 47	0.0015

Values are mean ± standard deviation.
Brackets indicated number of patients who reached that stage.
NS = not significant.

effect was considered to be present if the heart rate at rest decreased by 10% or more from placebo to atenolol phases. The tablets of atenolol and placebo were identical in appearance. Serum atenolol concentration was measured in 3 patients chosen at random at the end of the 2-week atenolol phase.

Exercise protocol: The 13 patients underwent exercise testing on a commercial treadmill according to a modified Bruce protocol until the point of exhaustion, dizziness or severe dyspnea was reached.

The following measures of functional capacity were compared during placebo and atenolol phases: (1) heart rate and blood pressure at rest, at the end of each exercise stage and at the completion of exercise; (2) total duration of exercise; and (3) maximal exercise capacity index (expressed as work units). Maximal exercise capacity was derived from the following formula, which was calculated for each stage of exercise and then summated: [time (min) × speed (km/hr) × incline (degrees)/3 minutes]. For example, in a patient who completed stage 1 but managed only 2 minutes of stage 2: $[(3 \times 2.7 \times 1)/3 + (2 \times 2.7 \times 5)/3] = 11.7$ work units. This index, adapted from Redfors,[10] takes into account not only the total time spent exercising, but also the increasing difficulty of exercise with each successive stage.

Plasma atenolol concentration: Atenolol concentrations were measured at random in 3 patients. The plasma concentration of atenolol was determined by the procedure described by Yin-Gail et al.[11]

Statistical analysis: Wilcoxon's signed-rank test procedure was used for analysis of all variables.[12] This test was modified where applicable according to the method of Bonferroni.[13] A p value of <0.01 was considered significant.

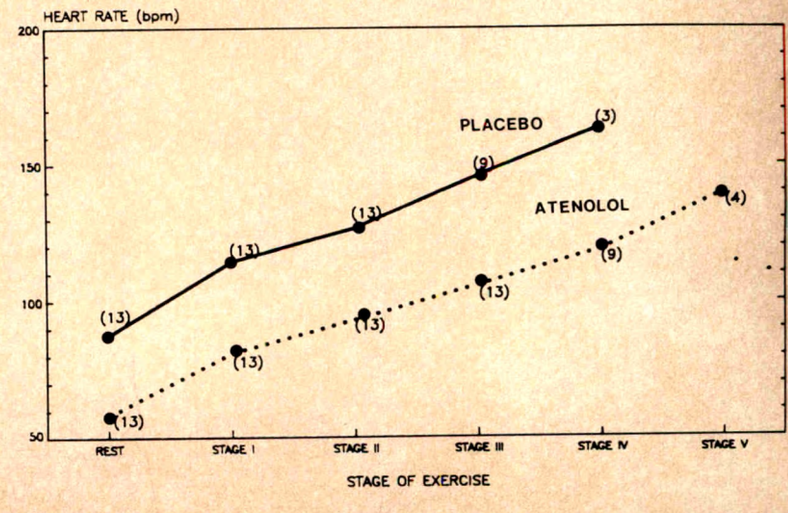

FIGURE 1. Mean heart rates at different stages of exercise during atenolol and placebo phases. **Brackets** indicate number of patients reaching a particular stage.

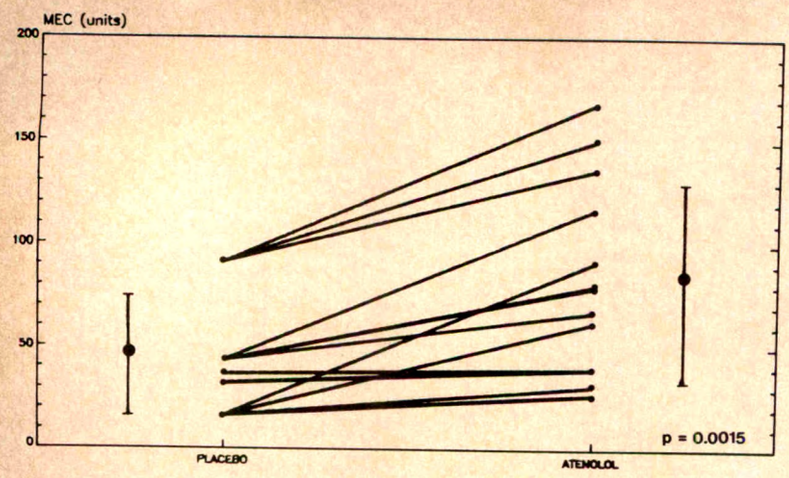

FIGURE 2. Maximal exercise capacity (MEC) during atenolol and placebo phases.

Results

Values at rest: Values measured at rest are listed in Table I. Mean heart rate at rest for the 13 patients was 88 ± 12 beats/min (range 57 to 100) during the placebo period, and decreased to 58 ± 8 beats/min (range 51 to 75) after 2 weeks of atenolol treatment ($p = 0.0015$). The mean decrease in heart rate at rest was 34%. Systolic and diastolic blood pressures did not change significantly.

Response to exercise: All individual and mean heart rates were significantly lower at each stage of exercise during atenolol treatment than during placebo (Fig. 1, Table I). Blood pressure values did not change significantly. The maximal exercise capacity and the total time spent on the treadmill increased significantly during the atenolol phase (Fig. 2 and 3, Table I).

Plasma atenolol concentration: The plasma atenolol concentrations in the 3 patients chosen at random were 193, 246 and 665 ng/ml (mean 368).

Discussion

The results of previous studies[3–8] reflecting acute hemodynamic changes in MS with SR strongly suggested that β-blocker administration on a long-term basis could improve exercise capacity. The only study that investigated this issue with oral therapy was not completely placebo-controlled and used a noncardioselective agent.[9] The present placebo-controlled study demonstrated that β blockade significantly improves exercise capacity in patients with MS and intact sinus node function. The results are similar to those of Penas et al.[9] The increase in exercise capacity is probably mediated by the negative chronotropic effect of β-blocking drugs on sinus node function, both at rest and in response to exercise. Effort dyspnea is reduced and the risk of exercise induced pulmonary edema is diminished.

Amery et al[14] showed that there is a clear relation between plasma atenolol concentration and percent reduction in exercise heart rate. The therapeutic plasma atenolol concentrations determined by these investigators (100 to 500 ng/ml) are similar to those obtained in the present study. In practice, the determination of plasma atenolol concentration is not necessary for the clinical management of compliant patients, although its availability permits the exclusion of placebo-related or conditioning effects. A decrease in heart rate of at least 10% at rest after a starting dose of 100 mg/day of atenolol is usually an adequate means of monitoring the compliance and clinical response of patients.

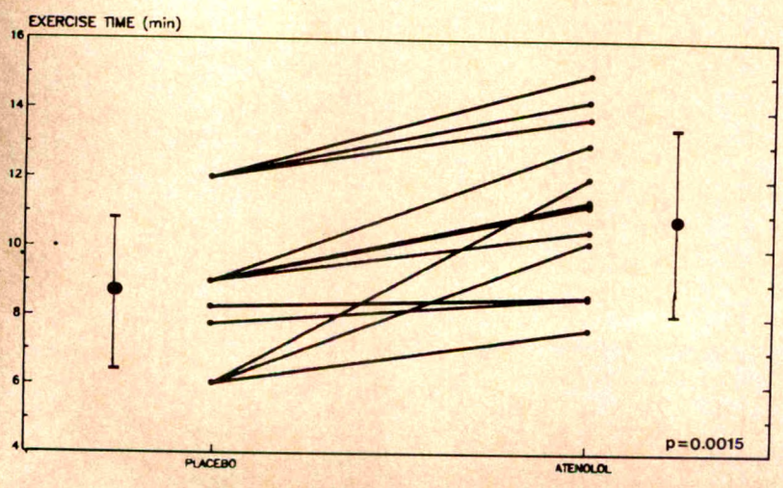

FIGURE 3. Exercise time during atenolol and placebo phases.

Physicians may be reluctant to use β-blocking drugs in patients with MS because of the negative inotropic effect of these drugs.[15,16] The deleterious effects of this action, however, in the context of MS without severe pulmonary arterial hypertension or evidence of right heart failure, is negligible.[4,5] The choice of atenolol was motivated by its easy (once a day) administration, as well as its long duration of action, cardioselectivity and hydrophilic properties. Although there is a potential and theoretical adverse effect of β blockade in reducing left atrial contractility, this effect was not evident in our patients or was negated by the advantageous effects of a slower heart rate.

Although the use of atenolol in pregnant and lactating women is limited, there is no evidence of teratogenicity, nor of neonatal or infant toxicity either in our experience or that of other investigators.[17–20] Outside of this study we have used atenolol in several pregnant women with MS without mishap.

Beta-blocking drugs should be administered cautiously when pulmonary arterial hypertension is marked, and their use may be contraindicated in some patients with MS and right ventricular failure.

The clinical application of this study is readily apparent. The long-term use of a β-blocking drug, such as atenolol will improve exercise capacity and allow the postponement of surgical intervention in many patients with significant MS.

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Electrophysiologic Mechanisms of Provoked Atrial Flutter in Mitral Valve Prolapse Syndrome

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To examine the electrophysiologic determinants of provoked atrial flutter (AF) in patients with mitral valve prolapse (MVP), studies were performed in 4 groups of patients: group 1 (n = 5), patients with MVP and AF; group 2 (n = 6), patients without MVP but with AF; group 3 (n = 6), patients with MVP but without AF; and group 4 (n = 5), patients without MVP and without AF. P-wave duration, intraatrial conduction, interatrial conduction and effective refractory periods for both the high right atrium and the low right atrium were longer in group 2 than in group 1. The effective refractory period of the low right atrium was longer in group 3 than in group 1. The interatrial conduction interval was longer in group 2 than in group 4. Thus, in patients without MVP, atrial conduction delay is the predominant determinant of AF, whereas differences in right atrial refractoriness appear to be most important to the provocation of AF in the patient with MVP. These differences in atrial refractoriness may be a result of abnormal autonomic influences in patients with MVP. **(Am J Cardiol 1985;56:602–604)**

Atrial flutter (AF) is a relatively common supraventricular arrhythmia generally associated with atrial enlargement[1] or atrial conduction disease.[2,3] Patients with mitral valve prolapse (MVP) in whom AF develops frequently do not have atrial enlargement. The role of atrial conduction and refractory period abnormalities in the development of AF in such patients is not known. To further delineate the electrophysiologic substrates of AF, the development of sustained AF to programmed atrial stimulation was compared in patients with and without MVP and no evidence of atrial enlargement.

Methods

Eighteen patients and 4 normal volunteers (16 women, 6 men), mean age 35 years (range 17 to 61), underwent electrophysiologic study for evaluation of suspected dysrhythmia or drug testing. All patients had palpitations, tachycardia, syncope or chest pain not typical for angina pectoris (Table I). The patients selected were those studied in chronologic order in whom atrial catheter positions were accurately known and AF was either readily reproduced in sustained fashion or was not inducible. The normal volunteers underwent electrophysiologic study related to a drug protocol. Electrocardiographic abnormalities were limited to ventricular premature complexes and nonspecific ST- and T-wave changes. Of the 24 subjects, in 11 MVP was diagnosed by classic auscultatory findings[4] and echocardiography.[5] In 11 patients MVP was excluded in a similar manner. Other than MVP, evidence of heart disease was absent. No patient had evidence of cardiomegaly or atrial enlargement by chest radiography and echocardiography. The echocardiographic criteria used for left atrial enlargement were those of Feigenbaum.[6]

For statistical analysis of the electrophysiologic data, the patients were classified into 4 subgroups based on the presence or absence of MVP and the presence or absence of AF. Group 1 consisted of 5 patients with MVP and provoked AF; group 2 consisted of 6 patients without MVP but with provoked AF; group 3 consisted of 6 patients with MVP but without AF; and group 4 consisted of 5 patients without MVP and without provokable AF. Two of 5 patients with MVP had spontaneous AF and 3 of 6 patients without MVP showed spontaneous AF or flutter-fibrillation (Table I). All groups were statistically similar in mean age.

Comparisons of electrophysiologic measurements were determined for group 1 vs groups 2, 3 and 4; group 2 vs group 4; and group 3 vs group 4.

All studies were performed in the postabsorptive, nonsedated state. Patients taking cardioactive drugs had medications discontinued at least 24 hours before the procedure. Beta-blocking drugs were discontinued at least 72 hours before the study. An esophageal bipolar catheter was positioned fluoroscopically at the level of the midleft atrium. A 6-pole catheter was inserted percutaneously and positioned for recording the His bundle potential. Bipolar or quadripolar catheters were inserted into the high and low right atrium. The high right atrial catheter was positioned anterolaterally near the superior vena cava and the low right atrial catheter in the low lateral right atrium near the inferior vena cava. Atrial pacing was accomplished using a programmed digital stimulator that delivered square-wave impulses at 1½ times the diastolic threshold and 2 ms in duration. Intracardiac electrograms were filtered at 40 to 500 Hz and recorded on an Electronics for Medicine recorder at paper speeds of 50 or 100 mm/s. Simultaneously, surface electrocardiographic leads I, aVF and V_1 were recorded.

Conduction intervals: P-wave duration was determined by measuring the onset to termination of the longest P wave

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TABLE I Clinical Descriptors, Atrial Conduction and Effective Refractory Periods in Groups 1 to 4

	Age (yr) & Sex	Symptoms	PWD	HR-LR	HR-L	ERP-HR	ERP-LR
			Group 1				
1	31F	Tach, syncope	73	21	35	240	170
2	24F	Syncope	79	22	42	200	190
3	36M	SVT	94	31	53	220	180
4	39F	LH, AF	65	31	48	220	170
5	43F	SVT, AF	76	21	29	220	170
Average ± SD			77 ± 11*	25 ± 5*	41 ± 10*	220 ± 14*	176 ± 9*,†,‡
			Group 2				
6	21M	Normal	98	27	53	270	210
7	26M	Normal	104	45	72	270	240
8	30M	Normal	90	45	53	220	210
9	26F	Syncope, AF	100	63	102	260	170
10	46F	Syncope, AF	90	40	62	270	210
11	42F	Probable AF	85	39	59	220	180
Average ± SD			94 ± 7*	43 ± 11*	66 ± 18*,‡	251 ± 25*	203 ± 25*
			Group 3				
12	25F	Syncope	80	19	71	240	280
13	55F	Chest pain, VPCs	86	32	55	230	220
14	25F	Palps	79	31	44	200	260
15	17F	Syncope	80	28	49	290	290
16	61M	Syncope	105	20	38	280	270
17	48F	Palps	95	30	41	260	240
Average ± SD			88 ± 10	27 ± 6	50 ± 12	250 ± 33	260 ± 26†
			Group 4				
18	19F	S/P ASD repair	70	25	39	210	190
19	52F	Syncope	100	38	50	220	200
20	46M	Palps	110	38	49	270	250
21	58F	SVT, LH	97	41	52	300	230
22	24F	Normal	95	23	40	250	270
Average ± SD			94 ± 15	33 ± 8	46 ± 6§	250 ± 38	228 ± 33§

* Group 1 vs 2 $p < 0.05$; † Group 1 vs 3 $p < 0.05$; ‡ Group 2 vs 4 $p < 0.05$; § Group 1 vs 4 $p < 0.05$.
AF = atrial flutter; ASD = atrial septal defect; ERP = effective refractory period; HR = high right atrium; L = left atrium; LH = lightheaded; LR = low right atrium; Palps = palpitations; PWP = P-wave duration; SD = standard deviation; S/P = status post; SVT = supraventricular tachycardia; Tach = tachycardia.

in electrocardiographic leads I, aVF or V_1. Right intraatrial conduction time was measured as the interval from high right atrial to low right atrial depolarization. The interatrial conduction time was the interval from the high right atrial to left atrial depolarization. The atrioventricular node and His-Purkinje conduction times were determined by measuring the low right atrium to His bundle and His bundle to ventricular depolarization intervals, respectively. The flutter cycle length was defined as the interval between 2 consecutive AF waves; the length of the flutter wave was the interval from beginning to end of the longest flutter depolarization in the high right, low right or left atrial recording.

Arrhythmia provocation and effective refractory periods: Arrhythmia provocation was performed by the extrastimulus technique applied to the high right and low right atria. Six to 8 atrial paced beats, A_1, at a rate of 100 beats/min, were followed by a premature stimulus, A_2. The A_1-A_2 interval was progressively shortened at 10-ms intervals until a sustained tachyarrhythmia was produced or A_2 no longer resulted in a subsequent atrial depolarization. This point was designated the effective refractory period. If pacing with a single premature stimulus did not result in a sustained tachyarrhythmia, A_2 was advanced 10 ms beyond the atrial effective refractory period and a second premature stimulus, A_3, was introduced at progressively premature intervals until a sustained tachyarrhythmia was produced or A_3 was found refractory. Sustained AF was defined as a regular atrial tachycardia at a rate of 250 to 350 beats/min lasting longer than 30 seconds. The arrhythmia was defined as absent if 1 or no repetitive responses developed.

Statistical methods: Measurements are presented as mean ± standard deviation. Comparisons between groups were performed using analysis of variance for a 2-way layout and the Student t test for unpaired data. A $p < 0.05$ was designated as statistically significant.

Results

Five patients with MVP and 6 without had sustained AF in response to programmed electrical stimulation. In patients in whom AF developed, the flutter cycle length and length of flutter wave were not different.

Group 1 (MVP, AV) versus group 2 (no MVP, AF): AH and HV intervals were not significantly different beween the 2 groups. However, when compared with group 1 patients, group 2 patients had longer P-wave duration, longer intraatrial and interatrial conduction intervals, and longer effective refractory periods for both high and low right atria (Table I).

Group 1 (MVP, AF) versus group 3 (MVP, no AF): Group 3 differed from group 1 only by the presence of

a longer effective refractory period of the low right atrium (Table I).

Group 1 (MVP, AF) versus group 4 (no MVP, no AF): Group 1 patients were similar in all measurements to group 4 patients except for a shorter effective refractory period of the low right atrium (Table I).

Group 2 (no MVP, AF) versus group 4 (no MVP, no AF): Interatrial conduction was longer in group 2 than in group 4 patients. All other measurements were not different (Table I).

Group 3 (MVP, no AF) versus group 4 (no MVP, no AF): No significant differences were found between the 2 groups for any of the electrophysiologic measurements.

Discussion

In several previous studies the electrophysiologic factors predisposing to the development of AF have been examined. Leier et al[2] showed that AF was associated with prolonged atrial conduction and an increased P-wave duration. Similarly, Watson and Josephson[3] found atrial conduction defects in 36 of 41 patients with sustained AF. Confirming these findings, our comparison of patients without MVP who had sustained AF vs those who did not have AF showed again that prolonged arial conduction was a marker or prerequisite for development of AF. In contrast, patients with MVP with provokable sustained AF did not show evidence of atrial conduction disease. In fact, compared with the group of patients without MVP who had AF, the MVP-AF group showed a distinct lack of atrial conduction and refractory period prolongation, displaying significantly shorter intraatrial and interatrial conduction times, shorter P-wave durations and shorter atrial effective refractory periods.

The patients without MVP who had AF had greater atrial conduction and refractory period prolongation than the patients with MVP who had flutter when compared with normal subjects. Although the MVP patient with provokable AF was electrophysiologically markedly different from the patient without MVP with AF, the MVP-AF patient different from the MVP patient without provokable AF only by the presence of a shortened low right atrial effective refractory period.

These findings suggest that different mechanisms are responsible for the production of AF in these 2 groups. The patients without MVP appear to have AF as a function of prolonged atrial conduction. Because patients with atrial enlargement were excluded and all groups were similar in age, the likely anatomic substrate is diffuse atrial fibrosis in this group.[7] On the other hand, the shorter low right atrial refractory period displayed by the MVP group who had AF suggests an inhomogeneity of refractory periods, especially since the high right atrial refractory periods were not different. However, multiple sites were not tested; this is required to document the increased temporal dispersion of refractoriness responsible for atrial reentry tachycardia.[8] The difference in atrial refractoriness present in the MVP patients with AF may be secondary to varying degrees of autonomic influence on the right atrial tissue. Gaffney et al[9] showed that MVP patients have an attenuated vagal response to the diving reflex. Prystowsky et al[10] showed that vagal stimulation shortened the effective refractory period of the human right atrium while producing shortening of the midright atrium in 1 patient. These observations may help to explain the disparities of atrial refractoriness noted in our patients. In addition, abnormalities in catecholamine metabolism in MVP patients have been previously reported.[11] These abnormalities alone or in combination with an abnormal vagal response could produce the changes in atrial refractoriness responsible for AF in patients with MVP.

The clinical significance of AF induced by means of premature stimulation in the laboratory is not totally clear. Comparing responses of patients with to without documented spontaneous AF or atrial fibrillation to single atrial extrastimuli, Engel et al[12] found vulnerability to flutter/fibrillation in 75% of those previously documented to have flutter/fibrillation and 36% of patients who were symptomatic (likely owing to dysrhythmias) but had not had atrial flutter/fibrillation during a recent 24-hour period of monitoring. This study did not mention atrial size and other descriptors of potential atrial abnormalities in either group of patients. Thus, although the group with documented atrial flutter/fibrillation would be the one more likely to have provokable flutter/fibrillation, both groups would be expected to have provokable arrhythmias. Studies performed on normal volunteers[13] have shown practically no tendency to flutter/fibrillation in response to single or double atrial extrastimuli. This finding, coupled with the documented contribution of atrial conduction disease to the development of AF, tend to make the disparate responses of the MVP patients, which appear potentially related to the different atrial effective refractory periods, all the more enlightening.

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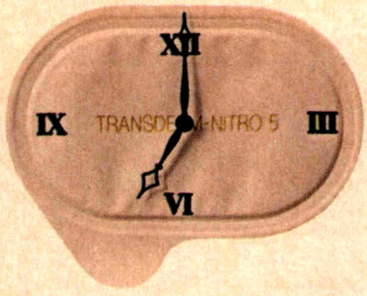

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This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

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Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

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Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.
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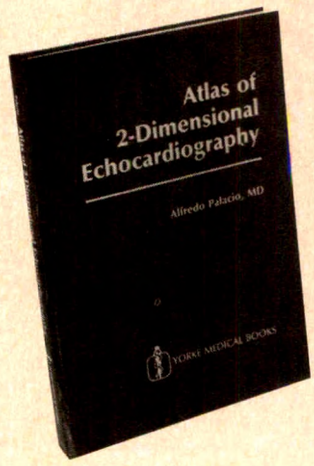

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Foreword by David H. Spodick, M
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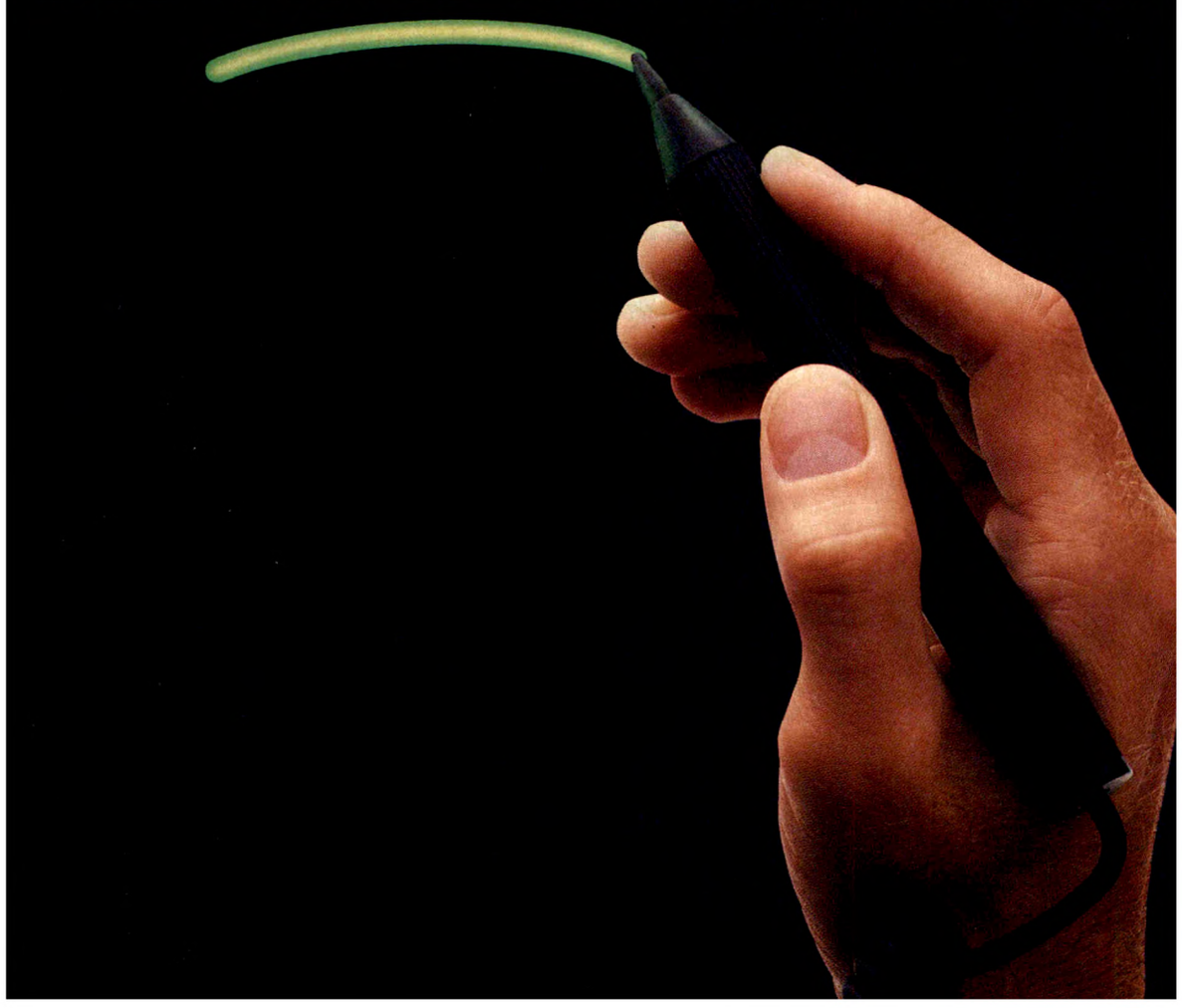

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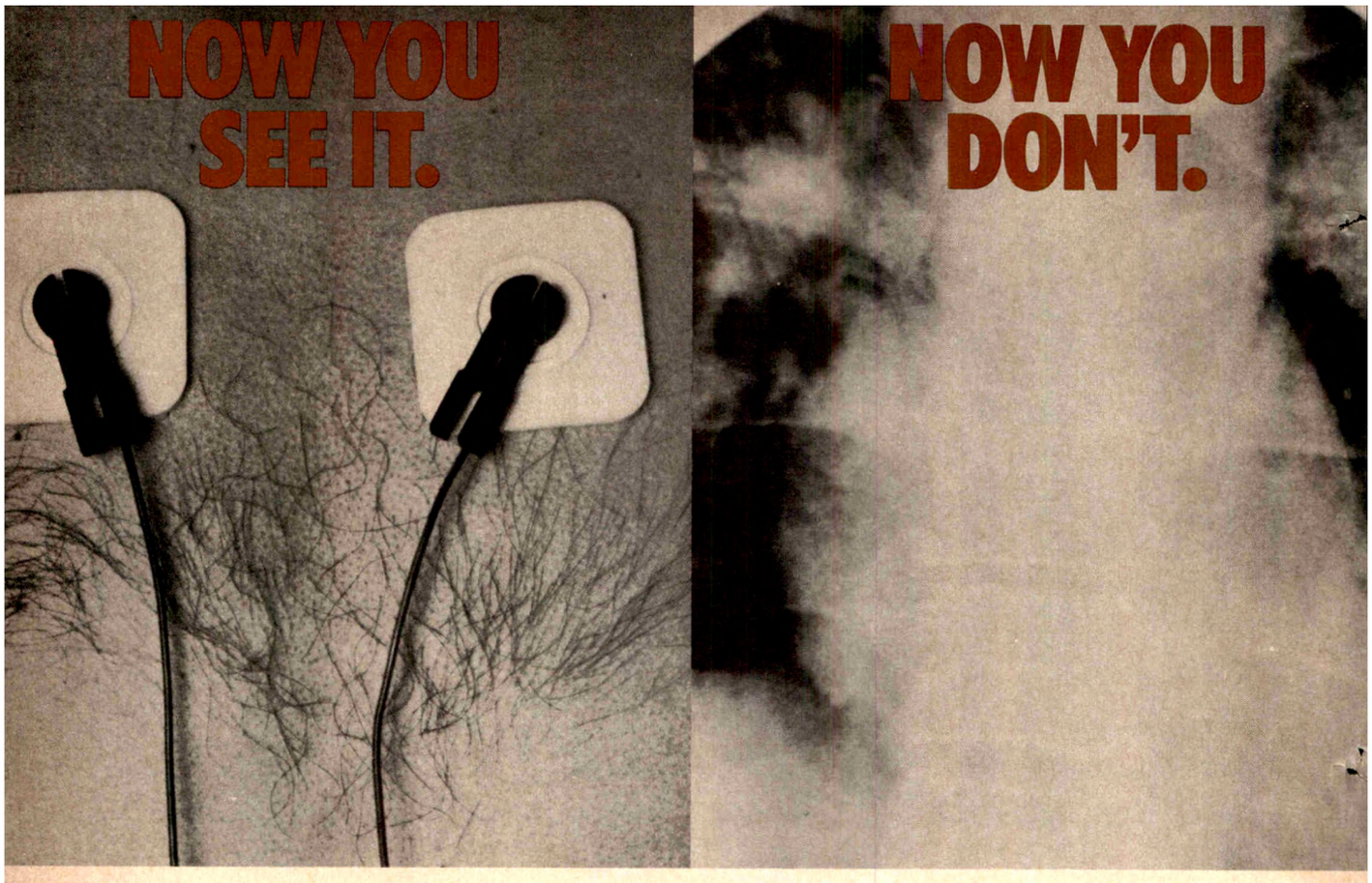

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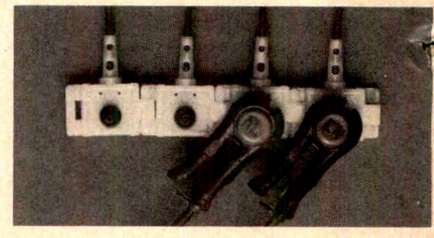

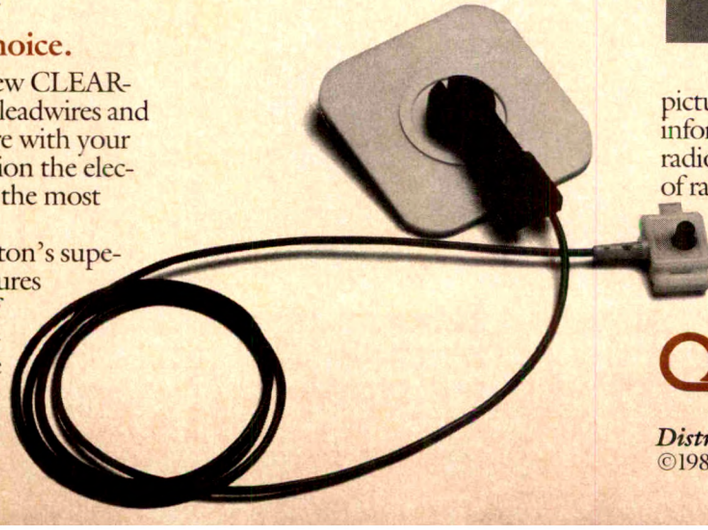

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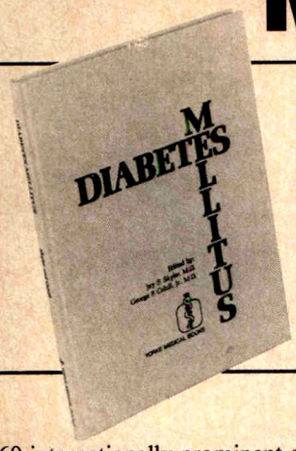

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CONTRAINDICATIONS
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ADVERSE REACTIONS
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Prognostic Significance of Exercise-Induced Left Ventricular Dysfunction in Chronic Aortic Regurgitation

DAVID S. GEE, MD, JACK E. JUNI, MD, JOHN T. SANTINGA, MD, and ANDREW J. BUDA, MD

Twenty-three patients with hemodynamically significant aortic regurgitation (AR) underwent gated equilibrium radionuclide angiography to assess rest and exercise left ventricular ejection fraction (LVEF) before and after aortic valve replacement. Preoperatively, LVEF decreased from 54 ± 3% at rest to 45 ± 3% during exercise ($p < 0.001$). Two patients died at operation. Postoperatively, after 5.7 ± 1.6 months, LVEF was 62 ± 5% at rest and 60 ± 4% during exercise (difference not significant). Exercise LVEF improved significantly postoperatively ($p < 0.01$). The patients were followed for a mean of 30 months (range 1 to 56), after valve replacement and during this period, 13 patients were in functional class I, 5 patients were in class II and 2 patients were in class III. One late death occurred and was unrelated to myocardial failure. Thus, in most patients with AR, exercise LVEF improves after aortic valve replacement. A preoperative decrease in LVEF during exercise in patients with significant AR does not predict a poor postoperative outcome. (Am J Cardiol 1985;56:605–609)

The timing of valve replacement in chronic aortic regurgitation (AR) is controversial. Several hypotheses have been proposed concerning the development of irreversible myocardial dysfunction in chronic AR and the identification of patients at high risk for surgical intervention.[1–11] Among these is the suggestion that a preoperative decrease in radionuclide left ventricular (LV) ejection fraction (EF) may predict a high-risk group of patients who may have subsequent deterioration in myocardial function after aortic valve replacement.[5–7] We evaluated the rest and exercise LVEF in patients with chronic AR before and after aortic valve replacement and assessed the prognostic significance of a preoperative exercise-induced decrease in LVEF.

Methods

Sixty-two patients were identified who had undergone aortic valve replacement between 1978 and 1982. Twenty-three of these patients met the criteria for inclusion in our study: (1) chronic AR with no other significant valvular disease, (2) preoperative rest and exercise radionuclide angiography performed within 4 months of valvular replacement, (3) cold potassium cardioplegia for myocardial preservation during valve replacement, and (4) no history of endocarditis or intravenous drug abuse.

Equilibrium gated radionuclide angiography was performed with in vivo labeling of red blood cells.[12,13] Patients performed symptom-limited, graded, supine exercise on a bicycle ergometer. Rest and peak exercise LVEF were calculated using a commercial semiautomated, edge-detection algorithm to determine background-corrected LV counts on a frame-by-frame basis. All preoperative radionuclide studies were done within 4 months of surgery and all postoperative studies were done no earlier than 6 months after valve replacement. Wall motion was assessed by consensus of 2 observers at rest and during peak exercise.

All patients underwent right- and left-sided cardiac catheterization preoperatively. In addition to supravalvular and biplane LV angiography, coronary arteriography was performed in all patients older than 40 years. AR was graded on a 4+ scale using standard criteria.[14]

All patients were interviewed concerning their current New York Heart Association functional status. The patient's functional status and medications being used were reviewed at that time. In addition, follow-up on any cardiac-related complications was determined.

Results are reported as mean ± standard error of the mean. Standard statistical techniques, including Pearson's correlation coefficient and t tests, were used.

Results

The results are tabulated in Table I. The study group included 15 men and 8 women, mean age 55 years (range 26 to 72). The mean known duration of AR was 29 months (range 0 to 144). The cause of AR was rheumatic heart disease in 13 patients, and bicuspid aortic valve with a perforated right cusp in 1 patient; the cause was unknown in 9 patients. Four patients had previous hospital admissions for congestive heart failure. The predominant symptoms were shortness of breath with exertion in 14 patients, chest pain in 7 patients, and syncope in 3 patients.

Preoperative cardiac catheterization data: All patients had at least grade 3/4 AR by aortic root cineangiography, with a mean severity score of 3.8. The mean cardiac output was 5.8 ± 1.6 liters/min and LV

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TABLE I Clinical and Functional Data

	Preoperative Data							Postoperative Data				
Pt	Age (yr) & Sex	Severity of AR	CAD	NYHA Class	Medications	Rest LVEF (%)	Exercise LVEF (%)	Outcome/Follow-Up Survival (mo)	NYHA Class	Medications	Rest LVEF (%)	Exercise LVEF (%)
1	56M	4+	−	I	0	42	41	Alive/16	I	0	N/A	N/A
2	69M	3+	−	III	Dig, D	74	60	Alive/56	I	0	72	59
3	26F	4+	−	II	Dig, D	68	70	Alive/24	I	0	57	62
4	63M	4+	−	II	Dig, D	23	27	Alive/46	I	Dig, D	15	17
5	61M	4+	+	II	0	64	50	Alive/15	I	0	88	84
6	49F	4+	−	II	Dig, D	77	68	Alive/49	I	D	77	65
7	48M	4+	−	I	0	59	47	Alive/5	I	Dig	59	50
8	69F	4+	−	II	Dig, D, BB	31	28	Alive/1	I	Dig	N/A	N/A
9	66F	4+	−	II	V, BB	56	43	Alive/25	I	0	N/A	N/A
10	53M	4+	−	I	V	55	35	Alive/32	I	0	N/A	N/A
11	70M	4+	+	I	V	46	40	Alive/28	I	0	56	60
12	35F	4+	−	I	0	63	59	Alive/23	I	Dig	N/A	N/A
13	54M	4+	−	I	0	47	42	Alive/60	I	0	74	69
14	59F	3+	+	IV	Dig, D, V	50	45	Alive/32	II	Dig, D, V	N/A	N/A
15	30M	4+	−	II	0	47	41	Alive/43	I	0	54	61
16	66M	4+	−	II	Dig, D	58	49	Dead/2	—	—	—	—
17	60M	3+	+	II	Dig	52	37	Dead/0	—	—	—	—
18	59M	4+	−	II	Dig, D, V	38	23	Dead/39	II	D, V	60	54
19	54M	3+	+	III	BB	57	37	Alive/52	II	BB	47	49
20	72M	4+	+	III	Dig, D	62	53	Alive/18	II	Dig, D	N/A	N/A
21	34F	4+	−	II	D	41	40	Alive/29	II	0	N/A	N/A
22	61M	4+	−	III	Dig, V	61	46	Alive/14	III	D	78	76
23	48M	3+	−	III	Dig, V, BB	68	68	Alive/21	III	BB	68	79

AR = aortic regurgitation; BB = β-blocking drug; CAD = coronary artery disease; D = diuretic; Dig = digitalis; LVEF = left ventricular ejection fraction; N/A = not available; NYHA = New York Heart Association; V = vasodilator.

end-diastolic pressure was 16 ± 2 mm Hg. Six patients had 70% or greater luminal stenosis of 1 or more major coronary arteries. Two patients each had 1-, 2- and 3-vessel disease.

Preoperative radionuclide angiographic data: Preoperatively, LVEF at rest was 54 ± 3%, and it decreased significantly with exercise to 45 ± 3% ($p < 0.001$) (Fig. 1). Only 2 patients, both in New York Heart Association functional class II, had an increase in LVEF, of 2% and 4%, respectively, with exercise. Analysis of LV wall motion showed that wall motion worsened with exercise in 12 patients, did not change in 10 patients and improved in 1 patient.

Surgical results: There was only 1 perioperative cardiac-related death: a 60-year-old man (patient 17) with 3-vessel coronary disease died of intractable ventricular tachyarrhythmias after an intraoperative myocardial infarct. Another patient, a 66-year-old man (patient 16), died of respiratory failure caused by bilateral phrenic nerve paralysis. Twenty-one patients had no significant perioperative complications.

Seven patients received Björk-Shiley prosthetic valves, 5 received Starr-Edwards valves and 11 received porcine valves. All patients with mechanical valves received anticoagulation therapy before discharge from the hospital. Of the 6 patients with coronary artery disease, 4 underwent concurrent coronary artery bypass operation.

Postoperative radionuclide angiographic data: In 13 of the 23 patients, postoperative rest and exercise radionuclide angiographic studies were performed. The studies were performed no earlier than 6 months after aortic valve replacement and at a mean of 9.2 months. Compared with preoperative values, there was no postoperative change in maximal rate-pressure product achieved (217 ± 10 vs 202 ± 14 mm Hg/min × 10^2, difference not significant [NS]). The postoperative LVEF at rest in these 13 patients was 59 ± 2%; it increased to 60 ± 4% during exercise (NS) (Fig. 2). Pre- and postoperative LVEF at rest in these 13 patients was not significantly different, 56 ± 4% vs 62 ± 5% ($p = 0.19$). However, there was a significant increase postoperatively in exercise LVEF, from 48 ± 4% to 60 ± 4% ($p < 0.01$) (Fig. 3). A comparison of pre- and postoperative wall motion abnormalities showed that there was improvement in 7 patients, no change in 3 patients, worsening in 1 patient, and inadequate technique precluded comparison in 2 patients. Exclusion of patients with significant coronary artery disease or coronary artery bypass grafts did not influence any of the postoperative results.

Clinical follow-up: The mean patient follow-up period of the 21 surviving patients was 30 months (range 1 to 56). The change in New York Heart Association functional class is shown in Figure 4.

There was only 1 late death, a 59-year-old man (patient 18) with Marfan syndrome who died after aortic root replacement 6 months after aortic valve replacement. Two patients with mechanical valves had cerebrovascular accidents despite therapeutic anticoagulation.

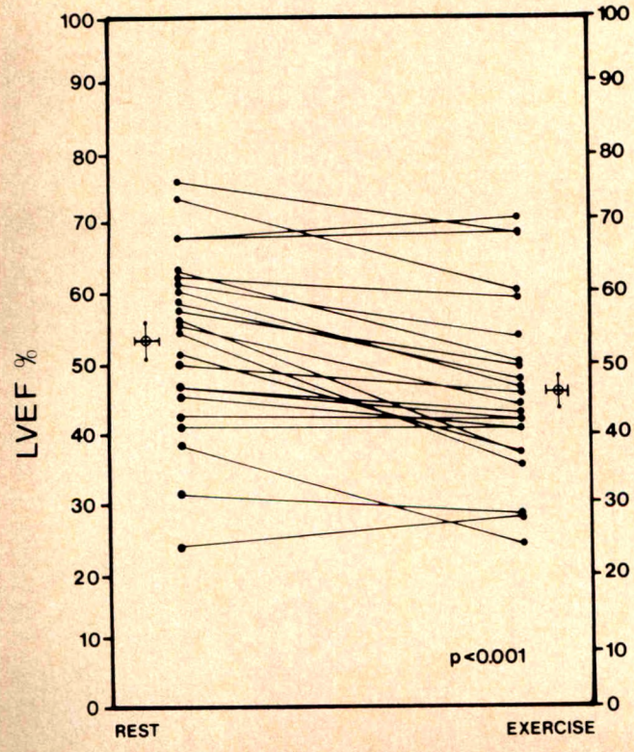

FIGURE 1. Preoperative change in left ventricular ejection fraction (LVEF) with exercise.

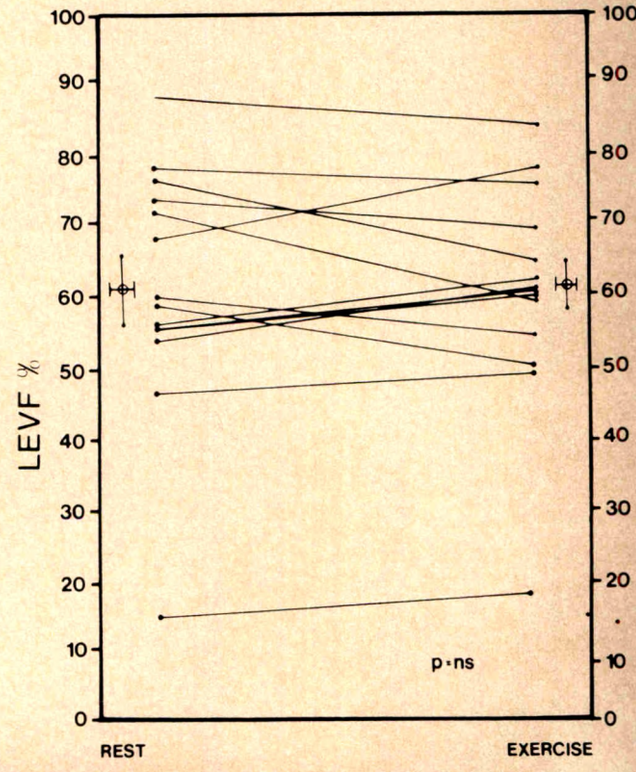

FIGURE 2. Postoperative change in left ventricular ejection fraction (LVEF) with exercise. NS = not significant.

Discussion

A major concern in chronic AR has been the development of irreversible myocardial dysfunction, which results in late death from congestive heart failure despite technically successful valve replacement. For example, 78% of late postoperative deaths from 1972 to 1978 at the National Institutes of Health (NIH)[9] were related to chronic congestive heart failure. As a result, several prognostic indicators related to LV dimensions and systolic function have been proposed to aid in the appropriate timing of surgery and in the identification of the high-risk patient who may respond poorly to valve replacement and have late congestive heart failure.[1–11]

In our study, all asymptomatic patients had a decrease in LVEF with exercise. Previous studies[5–7] have shown that most asymptomatic and symptomatic patients with chronic AR have an abnormal ejection fraction response during maximal supine exercise. It has been hypothesized that the decrease in radionuclide LVEF with exercise may represent an intermediate point between normal function and LV dysfunction at rest.[5] It has been further suggested that an abnormal exercise ejection fraction response may allow selection of patients for operation after ventricular function has begun to deteriorate, but before myocardial damage has progressed to the point at which postoperative prognosis is poor.[6] However, exercise is a complex intervention that induces changes in preload, afterload and contractility, which may affect ejection fraction variably in chronic AR.[15] Thus, it is difficult or impossible to differentiate a change in EF in chronic AR because of marked loading perturbations from that resulting from myocardial degenerative changes.

The primary finding in our study was that despite a decrease in preoperative exercise LVEF, patients with chronic AR had an excellent postoperative course. After a mean follow-up of 30 months, no patient who survived surgery had died or had congestive heart failure. These data suggest that exercise-induced LV dysfunction is compatible with a good long-term postoperative result and does not necessarily predict a poor postoperative course.

There is increasing evidence that exercise-induced LV dysfunction in symptomatic patients is often reversible after surgery.[7,16,17] In a consecutive series from 1976 to 1980, 93% of patients who underwent surgery at the NIH had an improvement in postoperative exercise LVEF.[7] In our series, there was a postoperative improvement in 64% of our patients. Unlike the NIH series, we did not find a significant improvement in the rest LVEF, probably because our patients had generally better LV function at rest than those of the NIH series. However, the long-term prognosis of patients who have an abnormal exercise LVEF before surgery has not been previously reported.

Our survival results after aortic valve replacement appear better than those previously reported.[7,18–20] This apparent improvement in survival has several possible explanations. First, all of our patients had cold potassium cardioplegia at the time of aortic valve replacement, which may have limited perioperative myocardial damage. Many data support the concept that advances in myocardial preservation techniques during surgery have improved postoperative survival.[3,21,22] Second,

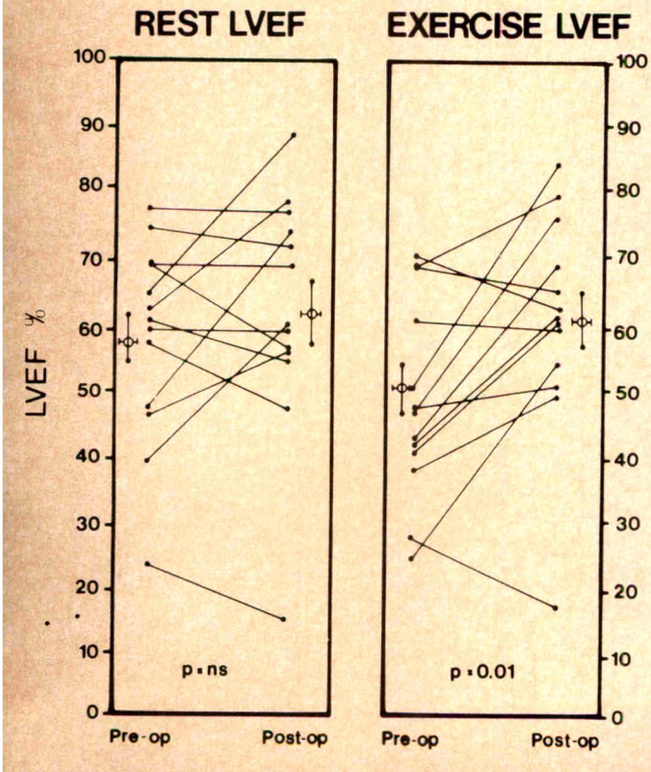

FIGURE 3. Comparison of preoperative and postoperative rest and exercise left ventricular ejection fraction (LVEF).

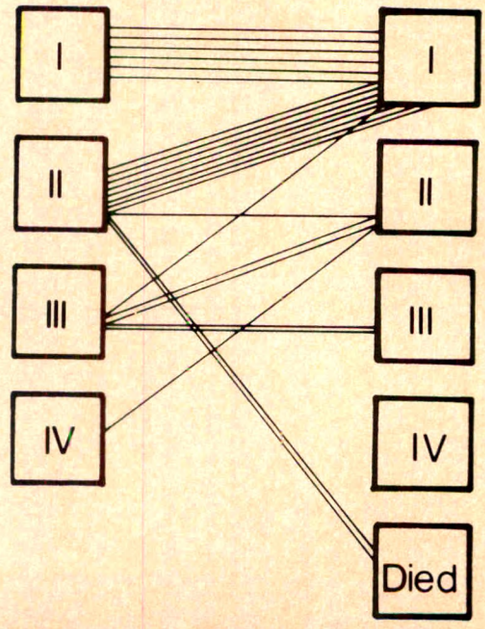

FIGURE 4. Changes in New York Heart Association functional class after valve replacement.

most of our patients with coronary artery disease underwent coronary bypass grafting. Myocardial revascularization may have improved long-term survival, although the benefits of coronary bypass grafting in patients with chronic AR remains controversial.[23] Third, exercise radionuclide abnormalities may have influenced the selection of patients for earlier operation; 6 of 23 patients were asymptomatic and 11 were only mildly symptomatic. Recent data from the NIH[17] suggest that there is a relation between the duration that LV dysfunction has existed and the likelihood that this dysfunction is reversible. Patients with earlier development of LV dysfunction are more likely to demonstrate normalization of LV function postoperatively than are patients whose LV dysfunction has been present longer than 1 year. None of our patients had serial radionuclide studies; thus, this relation may have influenced our survival results.

The precise role of the exercise EF response in patients with chronic AR remains to be determined. There are limited data on serial studies of rest and exercise LVEF in asymptomatic or symptomatic patients with chronic AR. Thus, the prognostic significance of a change in serial rest and exercise LVEF is uncertain. However, our data suggest that an exercised-induced abnormality in LVEF is common in patients being considered for aortic valve replacement and does not in itself predict a poor surgical result.

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Clinical and Echocardiographic Observations in Pulmonary Valve Endocarditis

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Clinical and echocardiographic data from 12 patients with pulmonary valve endocarditis are described. Seven patients had isolated pulmonary endocarditis and in 5 patients other valves were infected (aortic, tricuspid, mitral or all 3). Two patients were heroin addicts and 4 had underlying heart disease (congenital heart disease in 3 and aortic regurgitation in 1 patient). The organisms involved were *alpha streptococci* in 3 patients (all with underlying heart disease), *Staphylococcus aureus* in 4, *Streptococcus D bovis* in 1 patient and *Candida guillermondii* in 1. M-mode and 2-dimensional echocardiography was performed in 10 patients and revealed vegetations in 8. Pulsed Doppler echocardiography was performed in 6 patients and revealed pulmonary regurgitation in all 6. Seven patients had pulmonary emboli. Four patients underwent surgery. Four patients died, including 1 after cardiac surgery. Five patients, including the patient infected with *Candida guillermondii*, recovered with antibiotic treatment.

(Am J Cardiol 1985;56:610–613)

Pulmonary valve (PV) endocarditis is rare. Only 47 cases have been reported since 1960,[1–29] most of these being 1 or 2 cases of drug addicts or patients with congential heart disease. We report 12 patients with PV endocarditis.

Methods

Twelve cases of PV endocarditis were observed at Claude Bernard and Bichat Hospitals between 1972 and 1984. The diagnosis of PV endocarditis was made on the basis that septicemia was present and the PV was affected. PV involvement was confirmed by anatomic examination (surgery or autopsy), echocardiographic images of vegetations or by recent PV regurgitation diagnose by auscultation or pulsed Doppler echocardiography.

Echocardiography: Ten patients had echocardiographic examinations (M-mode and 2-dimensional [2-D] in 9 patients and M-mode alone in 1 patient). The echocardiographic examination was done either with a phased-array sector scanner (RT 400) with an M-mode type Irex II or with a mechanical sector scanner (ATL Mark 500) with a 3 MHz in-line transducer. PV recording was done in the short-axis view and the transducer was placed on the third or fourth intercostal space in a parasternal view visualizing the pulmonary outflow tract. The valves, the size of the right ventricle and septal motion were systematically examined using the usual methods. Several recordings were made during follow-up.

Diagnosis of vegetations was made when abnormal, shaggy, irregular echoes were seen on or near 1 or 2 pulmonary cusps and the motion of the cusps was not restricted.

Six patients underwent 2-D pulsed Doppler echocardiographic examinations with an ATL Mark 500 mechanical scanner. The sample volume (2 mm) was positioned along an M-mode line simultaneously with the 2-D image. For the PV examination, the sample volume was placed just below the pulmonary cusps in a short-view axis. PV regurgitation was demonstrated when abnormal positive diastolic turbulence was recorded toward the transducer and the pulmonary ejection signal moved away from the transducer.

Results

The clinical and bacteriologic results are summarized in Table I.

Clinical findings: The patients were 3 to 61 years old (mean 34). Eleven patients were men (92%). The patients were separated into 2 groups. Group I included 4 patients with underlying heart disease (congenital in 3). Group II included 8 patients with primitive PV endocarditis (2 heroin addicts, 2 alcoholics and 4 with no predisposing factors).

Seven patients (59%) had isolated PV endocarditis and in 5 patients other valves were infected (aortic in 1 patient, tricuspid in 2 patients, mitral in 1 and all 3 valves in 1).

Fever was present in all cases. A typical PV regurgitation murmur was found in only 3 patients (25%), all in group II. Associated aortic regurgitation masked the pulmonary auscultation in 2 other patients. One patient

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had right-sided congestive heart failure and 1 had left-sided heart failure. Seven patients (59%) had septic pulmonary emboli. The other signs of endocarditis were splenomegaly in 5 patients, arthralgia in 2, arthritis in 1 patient, purpura in 1 and proteinuria in 4.

The portal of entry was found in 7 patients (Table I).

Bacteriologic findings: Positive blood cultures were found in 9 cases: coagulase-positive staphylococci in 4 patients, including 1 methicillin-resistant case; *alpha streptococci* in 3; *Streptococcus D bovis* in 1; and *Candida guillermondii* in 1. Negative blood cultures were found in 3 patients who had taken antibiotics before hospitalization.

M-mode, 2-dimensional and pulsed Doppler echocardiography: Echocardiography revealed PV vegetations in 8 of 10 patients. However, for patients 3, 4, 7 and 8, the first echocardiogram, done on days 31, 14, 5 and 10, respectively, of the illness, yielded normal findings, although a typical diastolic murmur had been noted previously in patient 7. In addition, tricuspid valve fluttering was observed in patients 9, 10 and 11, and paradoxical septal motion with right ventricular hypertrophy in patients 9 and 10. Echocardiography did not reveal vegetations in patients 11 or 12. Patient 11 had only an M-mode echocardiogram, which did not visualize the PV. In patient 12 the 2-D echocardiogram was normal, but the M-mode echocardiogram revealed diastolic vibrations, suggesting valve impairment. The M-mode and 2-D echocardiographic results for patient 9 are shown in Figure 1. On day 30, the PV vegetation was visible; 48 hours later, the abnormal echoes had disappeared. This patient had had several episodes of pulmonary emboli. Images of PV vegetation disappeared in patient 2, and remained unchanged in the others.

Six patients had pulsed Doppler echocardiographic examinations. PV regurgitation was diagnosed in all 6. Figure 2 shows the pulsed Doppler echocardiogram from patient 12; a considerable diastolic flow suggestive of pulmonary regurgitation is visible.

Anatomic findings: Anatomic study was possible in 6 patients (2 autopsies and 4 operations). PV vegetations were found in all 6. Vegetations were also found on the right ventricle in patient 2, the tricuspid valve in patients 2 and 11, the mitral valve in patients 6 and 11 and the aortic valve in patients 4 and 11. The anterior pulmonary leaflet was destroyed in patient 1.

Treatment and clinical outcome: The illness lasted from 8 to 90 days (average 45). All patients were first treated with antibiotics 2 to 90 days (average 18) after the onset of illness.

In group I, 3 patients had cardiac surgery: patients 1 and 4 were cured with antibiotics and underwent surgery several months later to correct underlying heart disease; patient 2 had surgery after a 40-day course of antibiotic treatment, to correct heart disease, persistent large vegetations and repeated pulmonary emboli, and she recovered; patient 3 had leukemia and also mycotic endocarditis, which was cured by antibiotic therapy.

In group II only 1 patient (no. 11) had surgery, for left-sided heart failure owing to aortic regurgitation, but

TABLE I Clinical and Echocardiographic Data

Pt	Age (yr) & Sex	Predisposing Factors	Portal of Entry	Organism	PR Murmur	Other Murmur	Pulmonary Embolism	Other Valve Involvement	Echocardiogram (Vegetations)	Pulsed Doppler Echocardiogr.	Died
					Group I						
1	18M	T of F	Dental	*Alpha strep.*	0	0	0	0	PV	...	0
2	29F	PV stenosis	Dental	*Alpha strep.*	0	0	+	TV	PV, TV, Vent.	...	0
3	3M	VSD	Catheter	*Candida*	0	0	0	0	PV	PR	0
4	24M	AR	...	*Alpha strep.*	0	+(AR)	0	AV	PV, AV	AR, PR	0
					Group II						
5	57M	Alcoholic	...	0	0	0	+	0	...	...	+
6	61M	0	...	0	0	0	+	MV	...	...	+
7	27M	Opiates	IV	*Staph. aureus*	+	0	+	0	PV	PR	0
8	27M	Opiates	IV	*Staph. aureus*	+	0	+	0	PV	PR	0
9	9M	0	Catheter	*Staph. aureus*	0	0	+	0	PV	PR	0
10	31M	0	Cutaneous	*Staph. aureus*	0	0	+	0	PV	...	+
11	58M	Alcoholic	...	*Strep. bovis*	0	+(AR)	0	AV, TV, MV	AV, TV	...	+
12	59M	0	...	0	+	0	0	TV	0	PR, TR	0

AR = aortic regurgitation; AV = aortic valve; MV = mitral valve; PR = pulmonary regurgitation; PV = pulmonary valve; T of F = tetralogy of Fallot; TR = tricuspid regurgitation; TV = tricuspid valve; Vent. = ventricle; VSD = ventricular septal defect.

TABLE II Pulmonary Valve Endocarditis: Comparsion of Current Study Group with Published Cases

Category	Our Group (12 Cases)	Published Cases (47 Cases)
Incidence PV IE/Total IE	1.5%	1.7% (Roberts), 2% (Johnson)
Mean age (yr)	34	35
Primitive PV alone	5 (42%)	9 (19%)
Congenital heart disease	25%	51%
Opiate addiction	17%	32%
PR murmur	25%	61%
Pulmonary embolism	59%	61%
Right-sided CHF	8%	12%
Recovery	67%	59%

CHF = congestive heart failure; IE = infective endocarditis; PR = pulmonary regurgitation; PV = pulmonary valve.

he died of cardiac tamponade 14 days later. PV endocarditis was diagnosed at autopsy in patients 5 and 6. Patient 10 died suddenly after 24 days of antibiotic therapy, but autopsy was not possible. Four other patients were successfully treated with antibiotic therapy.

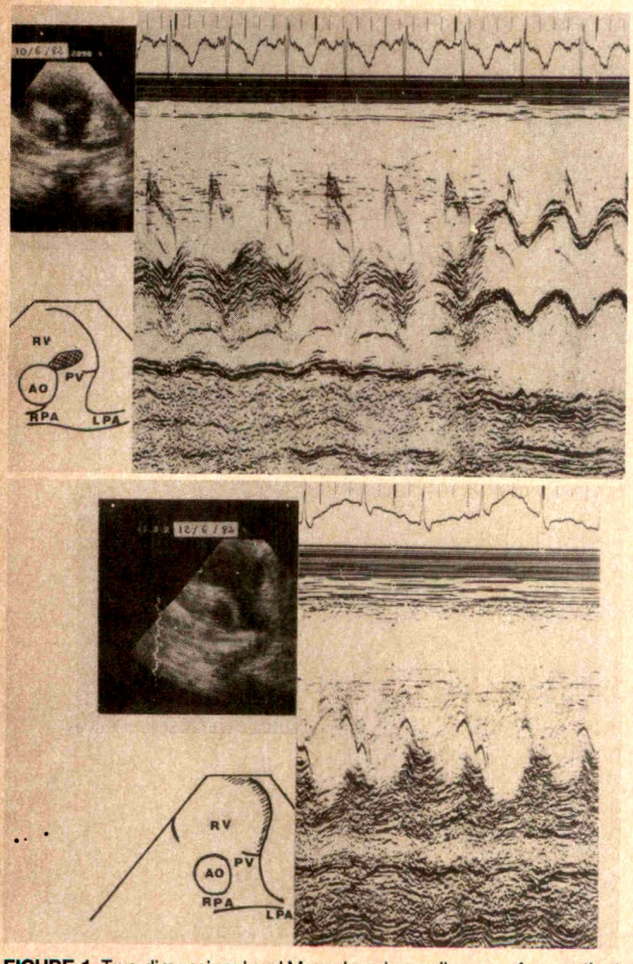

FIGURE 1. Two-dimensional and M-mode echocardiograms from patient 9. **Top,** day 30. A shaggy abnormal echo is present on the posterior pulmonary cusp. **Bottom,** day 32. The vegetation has disappeared. AO = aorta; LPA = left pulmonary artery; PV = pulmonary valve; RPA = right pulmonary artery; RV = right ventricle.

Surgery involved insertion of bioprostheses on the pulmonary and aortic valves for patient 4, resection of the PV in patient 1 and resection of PV vegetations in patients 2 and 11.

Discussion

The PV is the valve the least often involved in infective endocarditis. We found 47 reported cases since 1960 (Table II). However, the frequency of PV endocarditis apparently has increased. In our series, 10 of 12 cases were observed between 1982 and 1984, and the number of reported cases increases regularly. This is probably partly because of better diagnosis. In our study, PV endocarditis accounts for 1.5% of patients admitted for infective endocarditis. Roberts and Buchbinder[21] estimated that PV endocarditis accounts for 1.7% of fatal endocarditis cases; Johnson et al[1] reported that PV endocarditis accounts for 2% of endocarditis in subjects younger than 25 years. In addition, necropsy studies of endocarditis in heroin addicts[2,15,30] show that the PV is involved one-tenth as often as the tricuspid valve. Five of our patients (42%) had PV involvement alone without underlying heart disease. Only 9 patients (19%) so affected have been reported previously.[16–18,22–26] PV endocarditis was more common in patients with congenital heart disease[1–14] and in heroin addicts[2–11,15–20] than in our series (Table II).

When PV endocarditis affected a healthy heart, a virulent organism, often *Staphylococcus*, was usually found. However, when patients with congenital heart disease were affected, the causative organism was often alpha *Streptococcus*. *Gonococcus*, formerly considered to be a frequent organism in PV endocarditis,[31] is now seldom found; 2 cases have been reported since 1960.[25,26] To our knowledge, our patient 11 is the first case of myocotic PV endocarditis.

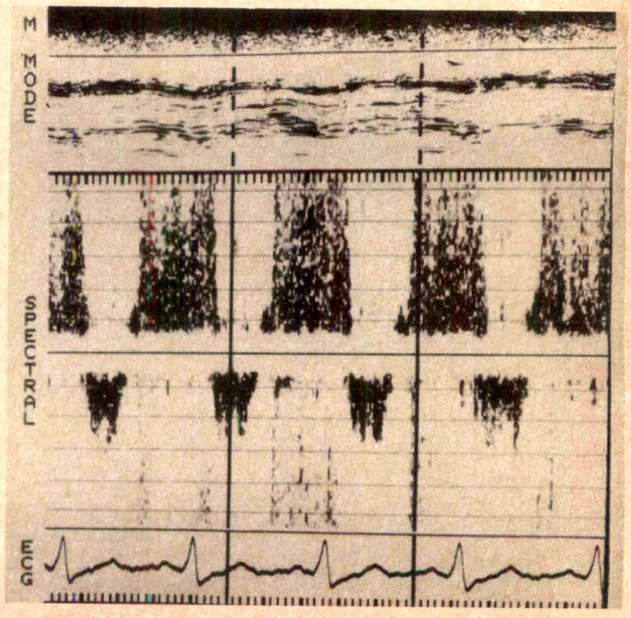

FIGURE 2. Pulsed Doppler echocardiogram from patient 12. Abnormal diastolic turbulence is recorded just below the pulmonary cusps.

More than half of the patients had pulmonary emboli (Table II). Diastolic murmur due to pulmonary regurgitation was not always detected; it may be masked by the murmur because of aortic regurgitation. Right-sided congestive heart failure was found in only 5 patients.[5,7,8,12] In 4 patients this was a result of partial or total obstruction of the PV caused by a large vegetation.

The first echocardiographic diagnosis of PV vegetation was by Kramer et al[20] in 1977. Since then, 16 cases have been reported,[2,13,14,17,18,20,25,26] 10 of which were confirmed by histopathologic study. In 2 of our patients the echocardiographic examination did not detect PV vegetations. Patient 9 did not undergo 2-D echocardiographic examination. Two-dimensional echocardiography is more sensitive than M-mode echocardiography for detecting PV vegetations.[14] PV vegetations were not visualized in patient 10, but valve impairment was. Vegetations can be observed a few days after the onset of symptoms, and often remain after the endocarditis has been cured.

In our study, tricuspid valve fluttering was not always observed in the diagnosis of pulmonary regurgitation (3 of 10 patients), but pulsed Doppler echocardiography was extremely sensitive (all 6 cases).

The clinical course of PV endocarditis depends mainly on which valves are associated. In other reports, the 10 patients with PV endocarditis and left-sided heart involvement[6,8,11,14,15,20,21,27–29] and the 7 patients with PV endocarditis and congenital heart disease[3,4,6,8,11,14] who did not undergo surgery died. However, 7 of 8 patients who received drug treatment for primitive PV endocarditis, whether isolated or associated with tricuspid endocarditis, recovered.[2,16,17,22,23,26]

In PV endocarditis without left-sided cardiac involvement or congenital heart disease, drug treatment usually suffices; surgery is advisable in the case of failure to treat bacterial infection or in right-sided heart failure (usually owing to obstruction of the PV). Pulmonary emboli do not, in our experience, justify surgery in PV endocarditis or in tricuspid endocarditis.[32] Surgery of the PV either involves excision of the vegetations or partial or total excision of the PV if it is destroyed. Residual pulmonary regurgitation is generally well tolerated.[23] Valve replacements are rarely carried out.

Acknowledgment: We thank Jane Alix for translating and typing the manuscript.

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Echocardiographic and Doppler Flow Observations in Obstructed and Nonobstructed Hypertrophic Cardiomyopathy

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Some investigators have suggested that left ventricular (LV) ejection is completed much earlier than normal in patients with hypertrophic cardiomyopathy (HC), whether or not a LV outflow gradient is present, and they have therefore concluded that LV ejection is not impeded in HC, but merely ends early because of early completion of LV emptying. This possibility was examined using pulsed Doppler echocardiography to record ascending aortic flow velocity patterns in 20 patients with HC, 12 with evidence of LV outflow gradient at rest (obstructed HC) and 8 without evidence of a significant resting gradient (nonobstructed HC). Peak aortic flow velocity was similar in patients with nonobstructed HC (92 ± 26 cm/s) and those with obstructed HC (94 ± 26 cm/s) and in 20 normal subjects (92 ± 11 cm/s). However, mean ejection time measured from the aortic flow velocity tracing or aortic echogram was longer in those with obstructed HC (345 ± 30 ms) than in those with nonobstructed HC (296 ± 24 ms, $p < 0.02$) and in normal subjects (294 ± 19 ms, $p < 0.01$). Furthermore, a rapid decrease in aortic flow velocity in midsystole was seen in 11 of 12 patients with obstructed HC, but in none of the patients with nonobstructed HC or normal subjects. Doppler left atrial flow velocity recordings, obtained in 11 patients, demonstrated mitral regurgitation in 4 of 5 patients with obstructed HC but in none of 6 patients with nonobstructed HC. The temporal relation between the decrease in Doppler aortic flow velocity, the peaking of Doppler mitral regurgitant flow, and the onset of mitral valve–septal contact in midsystole—as well as observations regarding LV internal dimensional changes—suggest that the early deceleration of aortic blood flow in the patient with obstructed HC is not merely a result of early completion of mechanical systole by a hyperdynamic left ventricle. Rather, midsystolic aortic flow deceleration is at least in part a result of the anterior leaflet of the mitral valve impeding LV outflow and causing ejection of blood by an alternate route into the left atrium. (Am J Cardiol 1985;56:614–621)

Studies of patients with hypertrophic cardiomyopathy (HC) and left ventricular (LV) outflow obstruction have shown that a greater percentage of blood than normal is ejected into the aorta by the left ventricle during the first half of systole.[1–6] One explanation for this finding is that blood is ejected normally in early systole, but by midsystole, subaortic obstruction occurs, which impedes ejection of blood into the aorta. A second explanation is that the left ventricle ejects most, if not all, of its blood volume in early systole, and therefore cannot eject more blood into the aorta in the second half of systole. Arguments for the second explanation are based on studies that suggest that in patients who have HC without LV outflow gradients (nonobstructed), LV ejection is completed early.[2,7]

To further examine the mechanism of LV ejection in patients with obstructed and nonobstructed HC, we used M-mode echocardiography (echo) and combined Doppler/2-dimensional (2-D) echo to evaluate the relation between changes in LV dimension, motion of the aortic and mitral valves, and blood flow velocity patterns in the ascending aorta and left atrium.

Methods

Patients: *Nonobstructed hypertrophic cardiomyopathy:* Eight patients (7 men, 1 woman) aged 14 to 67 years (mean

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TABLE I Clinical, M-Mode Echocardiographic and Doppler Characteristics

	Clinical				M-Mode			Doppler				
			LVOT Grad (mm Hg)									
Pt	Age (yr) & Sex	Fam Hx	Cath	Echo	VST (mm)	LVFW (mm)	VST/LVFW	HR (beats/min)	PFV (cm/s)	Avg Acc (cm/s)	ET ms	Dec Time Index (ms)
Nonobstructed HC												
1	25M	−	9	. . .	27	16	1.7	69	100	909	255	100
2	66M	−	ND	. . .	33	12	2.8	67	73	695	290	105
3	65M	−	0	. . .	24	08	3.0	54	77	700	320	115
4	28M	+	ND	. . .	21	09	2.3	66	115	1,095	285	95
5	14M	+	ND	. . .	22	07	3.1	63	142	1,352	280	90
6	33F	−	0	. . .	19	10	1.9	53	60	600	310	85
7	49M	+	ND	. . .	19	10	1.9	46	92	1,022	300	120
8	67M	+	0	. . .	25	15	1.7	50	80	1,230	330	60
Mean ± SD	43 ± 21		2 ± 4		24 ± 5	11 ± 3	2.3 ± 0.6	58 ± 9	92 ± 26	950 ± 272	296 ± 24	96 ± 19
Normal Subjects												
12M, 8F	28 (mean) 21–46 (range)		Mean ± SD		10 ± 1	9 ± 1	1.1 ± 0.1	62 ± 10	92 ± 11	940 ± 161	294 ± 19	94 ± 12
Obstructed HC												
1	26F	+	ND	67	25	9	2.8	66	107	973	315	85
2	50M	−	ND	56	24	14	1.7	70	67	893	340	45
3	23F	+	60	56	20	10	2.0	72	101	1,122	340	55
4	34M	+	80	68	24	13	1.8	44	60	706	395	60
5	70F	−	ND	42	22	13	1.7	66	85	1,214	390	50
6	40F	−	ND	68	26	9	2.9	56	105	1,167	305	90
7	62M	+	80	69	28	12	2.3	50	112	1,493	305	40
8	16F	−	ND	56	32	11	2.9	58	70	737	335	85
9	26M	+	ND	47	32	14	2.3	66	79	832	360	100
10	37F	+	160	147	22	12	1.8	78	140	1,120	350	75
11	55M	+	ND	51	31	10	3.1	71	72	800	340	40
12	26F	+	ND	64	30	13	2.3	76	135	1,421	370	45
Mean ± SD	39 ± 17		95 ± 44	66 ± 27	26 ± 4	12 ± 2	2.3 ± 0.5	64 ± 10	94 ± 26	1,040 ± 259	345 ± 30	64 ± 22

Avg Acc = average acceleration; Cath = cardiac catheterization; Dec = deceleration; ET = ejection time; Fam Hx = family history; HC = hypertrophic cardiomyopathy; HR = heart rate; LVFW = left ventricular free wall thickness; LVOT = left ventricular outflow tract gradient at rest; ND = not done; PFV = peak flow velocity; SD = standard deviation; VST = ventricular septal thickness; + = present; − = absent; . . . = not applicable.

43), constitute this group (Table I). All patients had M-mode echocardiograms that showed asymmetric septal hypertrophy; specifically, a ventricular septal thickness of more than 18 mm and a ratio of ventricular septal to LV free wall thickness of more than 1.3 to 1 when thicknesses were measured in diastole below the mitral leaflet tips (Table I). Although some patients had mild systolic anterior motion (SAM) of the mitral valve in systole, in no patient was it severe enough to cause the mitral leaflet to come close to contacting the ventricular septum in systole. The presence of asymmetric septal hypertrophy was confirmed in all patients by 2-D echo. Four of the 8 patients had at least 1 family member with documented HC. Four patients underwent cardiac catheterization which confirmed, in all 4 cases, the absence of a significant (more than 10 mm Hg) LV outflow tract gradient at rest. In addition, all 4 had less than a 30 mm Hg gradient after provocative maneuvers such as isoproterenol, amyl nitrite, the Valsalva maneuver and postpremature ventricular beat. All 4 also underwent LV angiography, which demonstrated a thick-walled left ventricle with near obliteration of the cavity at end-systole. Thus, 7 patients had either a positive family history or catheterization confirmation of the disease. Two patients with nonobstructed HC were taking β-blocking drugs (propranolol), but none was taking calcium-channel blockers.

Obstructed hypertrophic cardiomyopathy: The group of patients with obstructed HC consisted of 5 men and 7 women, aged 16 to 70 years (mean 39). All 12 patients had an M-mode echo demonstrating asymmetric septal hypertrophy and SAM of the mitral valve sufficient to produce prolonged systolic contact between the anterior mitral leaflet and the ventricular septum.[8–10] The echo time period index proposed by Pollick et al[10] was used to estimate the LV outflow tract gradient by the following equation: Pressure gradient (mm Hg) = 25 (index) + 25, where index = duration of SAM–septal contact (ms) divided by the time from onset of SAM to onset of SAM–septal contact (ms) (Table I). The presence of asymmetric septal hypertrophy and septal–mitral contact during systole was confirmed by 2-D echo in all patients.

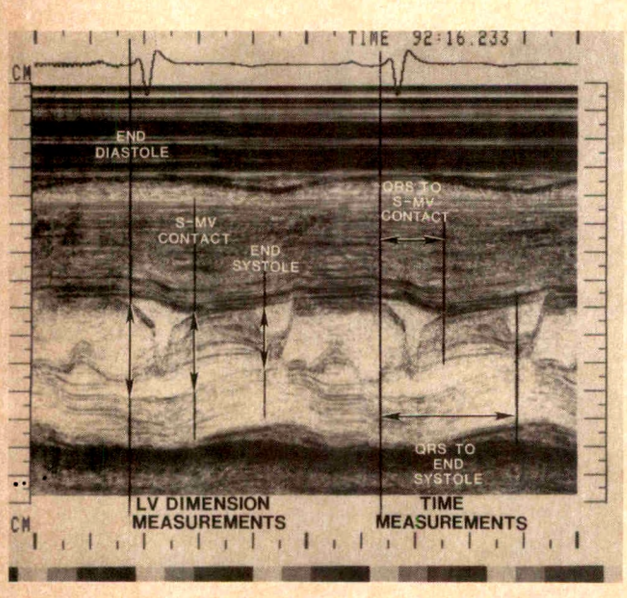

FIGURE 1. M-mode echocardiogram from patient 4, with obstructed hypertrophic cardiomyopathy, labeled to demonstrate left ventricular (LV) dimensional and time measurements. Asymmetric septal hypertrophy and systolic anterior motion of the mitral valve are present. S-MV = ventricular septal–mitral valve.

Eight of the 12 patients had at least 1 family member with documented HC. Four patients in this group had undergone cardiac catheterization and each had an LV outflow gradient at rest of 30 mm Hg or greater (Table I). Eleven patients with obstructed HC were taking β-blocking drugs (propranolol); none was taking calcium-channel blockers.

Normal subjects: Doppler data obtained in the patients with obstructed and nonobstructed HC were compared with data previously obtained in 20 normal subjects. These normal subjects consisted of 12 men and 8 women, ages 21 to 46 years (mean 28).[11]

M-mode echocardiography: M-mode echocardiograms were obtained in the supine or left lateral decubitus positions using a 2.25-MHz, medium-focus transducer with a commercially available echocardiographic module interfaced to a strip-chart recorder (Fig. 1). Ventricular septal and LV free wall thickness and LV internal dimensions were measured in all patients and normal subjects as recommended by the American Society of Echocardiography.[12] In the 12 patients with obstructed HC, 2 additional measurements were made, the time from onset of the QRS complex to initial contact between the mitral valve and the ventricular septum and LV internal dimension at the time of initial contact between the mitral valve and the ventricular septum (Fig. 1).

In 11 of the 12 patients with obstructed HC, adequate M-mode echograms of the aortic valve were obtained. From these echograms, measurements were made from the onset of the QRS complex to the onset of aortic valve opening, maximal midsystolic partial closure of the aortic valve leaflets, and aortic valve closure.

Stop-frame images of the mitral and aortic valve echograms were recorded in the patients with HC at the equivalent of 100 mm/s paper speed.

Doppler echocardiography: All Doppler echo studies were performed with patients at rest using a commercially available ultrasound instrument (Electronics for Medicine/Honeywell Corp.). Using a mapping technique previously described, pulsed Doppler flow velocity recordings were made in the ascending aorta in all 20 patients with HC and 20 normal subjects[11] (Fig. 2). The aortic flow velocity signal used for analysis was that characterized by the greatest maximal flow velocity.

Peak aortic flow velocity, acceleration time, average acceleration, ejection time and a deceleration time index were measured in all patients and normal subjects.[11] Peak flow velocity was determined as the midpoint of the Doppler flow spectrum at the time of maximal flow velocity. Acceleration time was measured from the onset of ejection to the time of peak flow velocity. Average acceleration was calculated by dividing peak flow velocity by acceleration time. Ejection time was measured from the onset to the end of ejection. In 5 patients, 3 with obstructed HC, the end of ejection was difficult to determine from the Doppler aortic flow velocity tracings. In these 5 patients, data for the ejection time were taken from the aortic valve echogram. A Doppler deceleration time index was measured as the time required to decelerate from peak flow velocity to 75% of peak flow velocity. In addition, each aortic flow velocity curve was examined for the presence or absence of a contour characterized by a marked decrease in aortic flow velocity in midsystole with a low flow velocity in mid- to late systole.

In 5 patients with obstructed and in 6 with nonobstructed HC, Doppler flow tracings were recorded behind the mitral valve in the left atrium using an apical 2-chamber or apical 4-chamber 2-D echo image (Fig. 2). Left atrial flow velocity recordings were examined for evidence of mitral regurgitation as indicated by abnormal systolic retrograde flow into the left atrium. In 9 additional patients, left atrial flow velocity could not be measured from the apical approach because the range

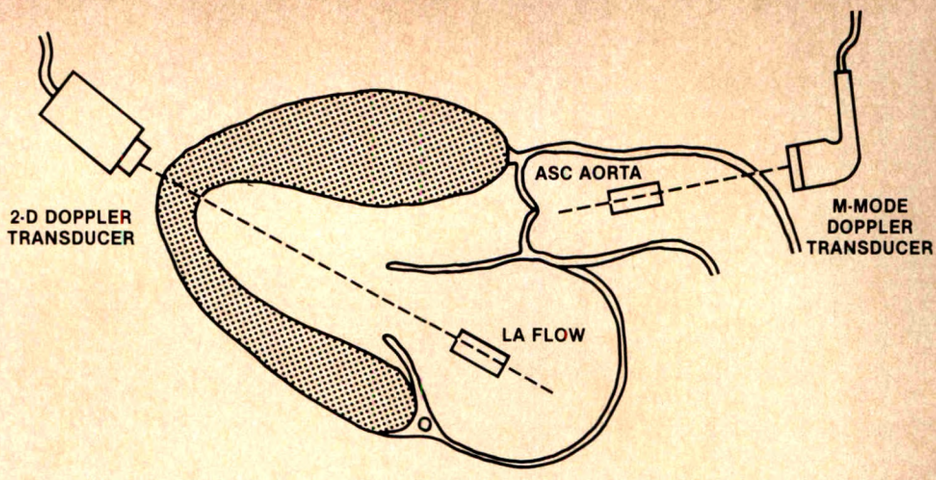

FIGURE 2. Method of recording flow velocity patterns in the ascending (ASC) aorta and left atrium (LA). Two-dimensional (2-D) echo imaging in an apical 2-chamber (or 4-chamber) view is used to position pulsed Doppler sample volumes in the left atrium, whereas a "mapping" technique (without imaging) is used to record ascending aortic flow velocity.

of our pulsed Doppler instrument limited flow recording to a maximal sample depth of 16 cm.

Statistical comparisons: Comparisons of Doppler data among the 3 subgroups (normal subjects, patients with nonobstructed HC and those with obstructed HC) were made using an analysis of variance. A Student t test was used to compare aortic and mitral valve echo timing measurements, or aortic valve echo and Doppler aortic flow timing measurements in the same patient.[13]

Results

Table I is a summary of some of the clinical, M-mode echocardiographic and Doppler data in the patients with obstructed and nonobstructed HC. The septal

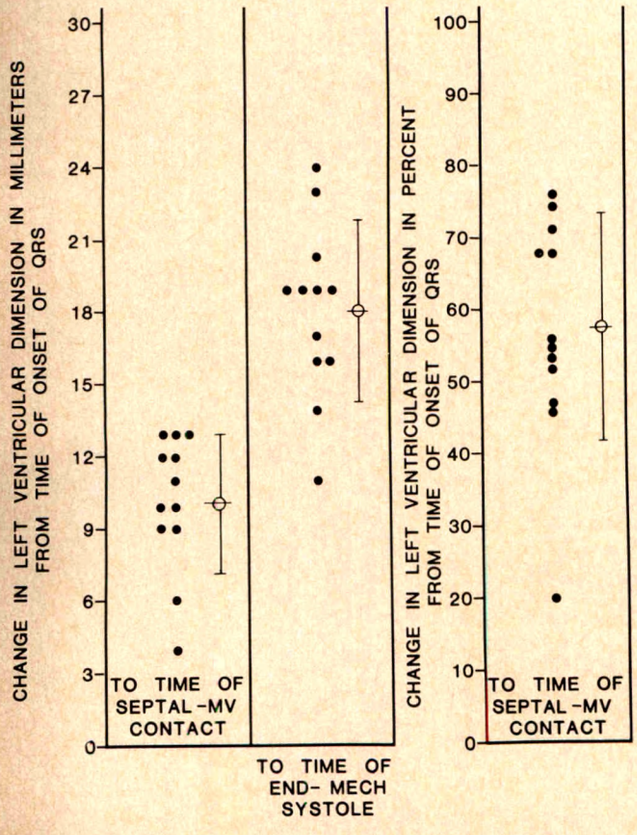

FIGURE 3. Relation between onset of systolic mitral valve (MV)–septal contact and left ventricular (LV) internal dimensional changes in 12 patients with obstructed HC. **Left,** change in LV dimension from time of onset of the QRS complex to time of initial MV–septal contact. **Middle,** change in LV dimension occurring from onset of the QRS to end of mechanical systole. **Right,** change in LV dimension from onset of the QRS to the time of septal–MV contact as a percent of total change in LV internal dimension that occurs from time of onset of QRS to end of mechanical systole. Mean ± SD is shown to the right of each panel.

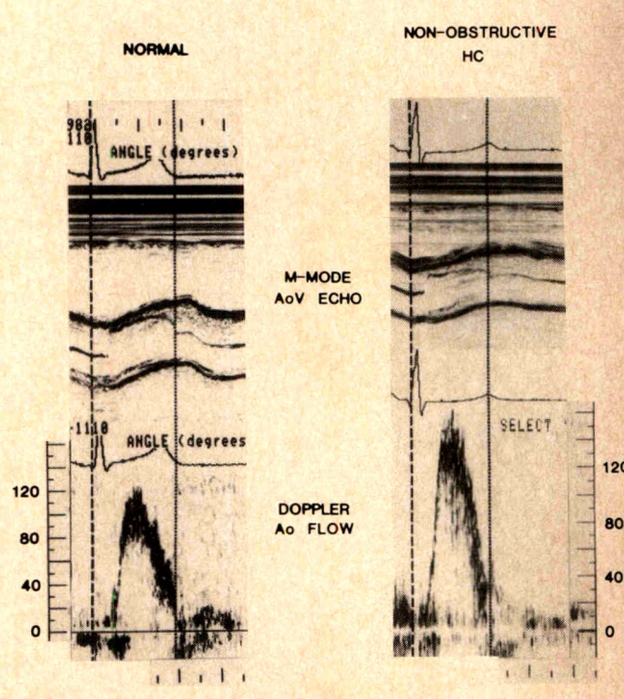

FIGURE 4. Left, aortic valve (AoV) echogram (**top**) and ascending aortic (Ao) flow velocity recording (**bottom**) in a normal subject. Echocardiographic and Doppler flow velocity recordings are matched so that the preceding RR intervals are within 20 ms of each other. **Vertical lines** are drawn at approximately the onset of the QRS complex and at the time of aortic leaflet closure on the aortic valve echogram. Aortic flow begins simultaneous with aortic valve opening, has a smooth limb of acceleration and reaches peak velocity before midsystole. Normal deceleration exhibits a somewhat wider spectrum of flow velocities, but a smooth contour, and ends simultaneous with aortic valve closure. **Right,** aortic valve echogram (**top**) and aortic flow velocity recording (**bottom**) from the same patient as in Figure 2, with nonobstructed hypertrophic cardiomyopathy. Midsystolic partial closure is absent on the aortic valve echogram and there is a normal aortic flow velocity contour.

thickness was at least 19 mm and the septal–free wall ratio was at least 1.7 in each of these patients.

Left ventricular dimensional changes in obstructed hypertrophic cardiomyopathy: Figure 3 shows the relation between SAM of the mitral valve and changes in the LV dimension (minor-axis shortening) in the patients with obstructed HC. The average change in LV dimension at the onset of septal–mitral valve contact as a percent of the total LV dimensional change during electromechanical systole was 58% (range 20 to 76%).

Doppler aortic flow velocity recordings: *Normal subjects and patients with nonobstructed hypertrophic cardiomyopathy:* Figure 4 shows aortic flow velocity tracings and aortic valve echograms from a normal subject and a patient with nonobstructed HC. Aortic flow velocity patterns and aortic valve echograms in both cases have the same contours and temporal relation. Specifically, aortic flow begins at the time of aortic valve opening and shows a smooth acceleration phase to a peak velocity occurring before midsystole. The deceleration phase also exhibits a smooth contour—without a midsystolic rapid deceleration in flow velocity—and ends at the time of aortic valve closure. There is no midsystolic partial closure present on either aortic valve echogram. Aortic peak flow velocity, average acceleration, ejection time and deceleration time index were not significantly different between the normal subjects and the patients with obstructed HC (Table I).

Patients with obstructed hypertrophic cardiomyopathy: In contrast to the normal subjects and patients with nonobstructed HC, a rapid decrease in aortic flow velocity was noted in midsystole in 11 of 12 patients with obstructed HC (Fig. 5 and 6). One patient with

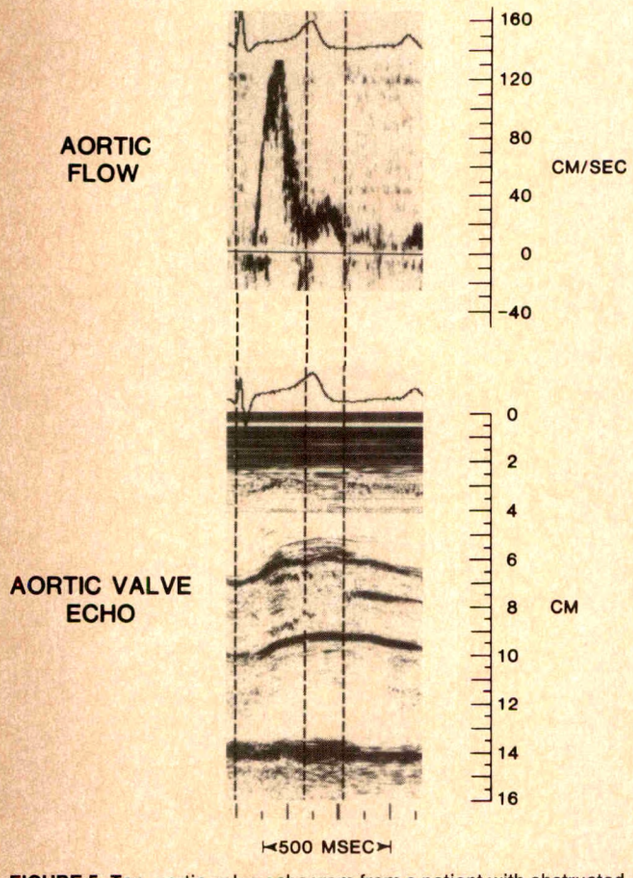

FIGURE 5. Top, aortic valve echogram from a patient with obstructed HC; **bottom,** aortic flow velocity tracing from the same patient. The aortic valve echogram and flow velocity recording are matched so that the preceding RR intervals are within 20 ms of each other. Characteristic partial midsystolic closure is seen on the aortic valve echogram. **Vertical lines** are drawn at the time of onset of QRS complex, Doppler aortic midsystolic flow velocity nadir, and end of ejection on the Doppler flow velocity tracing. The nadir in midsystolic aortic flow velocity occurs at about the time of maximal midsystolic partial closure of the posterior aortic leaflet (noncoronary cusp), but well before aortic valve closure. The end of ejection on the Doppler tracing occurs nearly simultaneous with aortic valve closure.

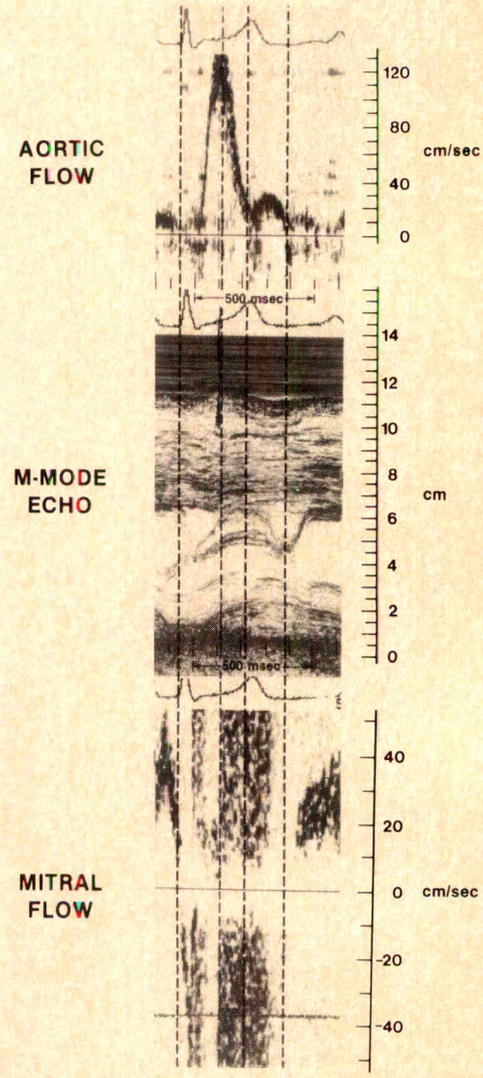

FIGURE 6. Temporal sequence of systolic events in obstructed hypertrophic cardiomyopathy. **Dashed vertical lines** are drawn at the onset of QRS, onset of systolic anterior motion–septal contact, midsystolic aortic flow velocity nadir, and end of ejection on the aortic flow velocity recording. Flow velocity recorded in the left atrium near the level of the mitral valve shows turbulent systolic flow consistent with mitral regurgitation (**bottom**). M-mode echocardiogram at the level of the mitral valve shows septal–mitral valve contact (**middle**). Ascending aortic flow velocity recording shows a rapid midsystolic flow velocity deceleration (**top**). These 3 records, from patient 12, were matched such that the preceding RR intervals were within 20 ms of each other.

obstructed HC had a normal-appearing aortic flow velocity contour without a rapid decrease in flow velocity in midsystole.

Mean heart rate, peak aortic flow velocity and average acceleration were not statistically different in the 3 groups (Table I). However, mean ejection time was greater in patients with obstructed HC (mean 345 ± 30 ms) than in those with nonobstructed HC (296 ± 24 seconds, $p < 0.02$) and the normal subjects (294 ± 19 ms, $p < 0.01$) (Fig. 7). There was no significant difference in ejection time between the patients with nonobstructed HC and normal subjects, even after ejection time was corrected for heart rate using a formula described by Weissler et al[14] for external carotid pulse tracings.

We also measured ejection time from the aortic valve echogram in the same patients (Fig. 4 and 5). Paired measurements of ejection time calculated from Doppler aortic flow tracings and from aortic valve echograms were not significantly different. In 13 of the 14 patients, ejection time measured by the 2 methods did not differ by more than 20 ms.

Data for the deceleration time index, summarized in Table I, reflect a significantly shorter index in patients with obstructed HC (64 ± 22 ms) than in those with nonobstructed HC (96 ± 19 ms) or normal subjects (94 ± 12 ms) ($p < 0.001$). This difference reflects the more rapid early deceleration of aortic flow velocity in patients with obstructed HC.

M-mode echo/Doppler aortic flow relationships in obstructed hypertrophic cardiomyopathy: Figure 8 is a summary of the temporal relations between the onset of mitral valve–septal contact, aortic valve midsystolic partial closure, the initial nadir in Doppler flow velocity and total electromechanical systole as measured from the onset of QRS to end of ejection. In the 11 patients with obstructed HC and rapid midsystolic decrease in aortic flow velocity, the time from onset of QRS to initial systolic contact of mitral valve and septum averaged 218 ms (range 135 to 300), while the time from onset of QRS to maximal midsystolic partial closure of aortic valve leaflets averaged 244 ms (range 155 to 350). These 2 measurements were statistically similar and suggest that the onset of septal–mitral valve contact and midsystolic partial closure on the aortic valve

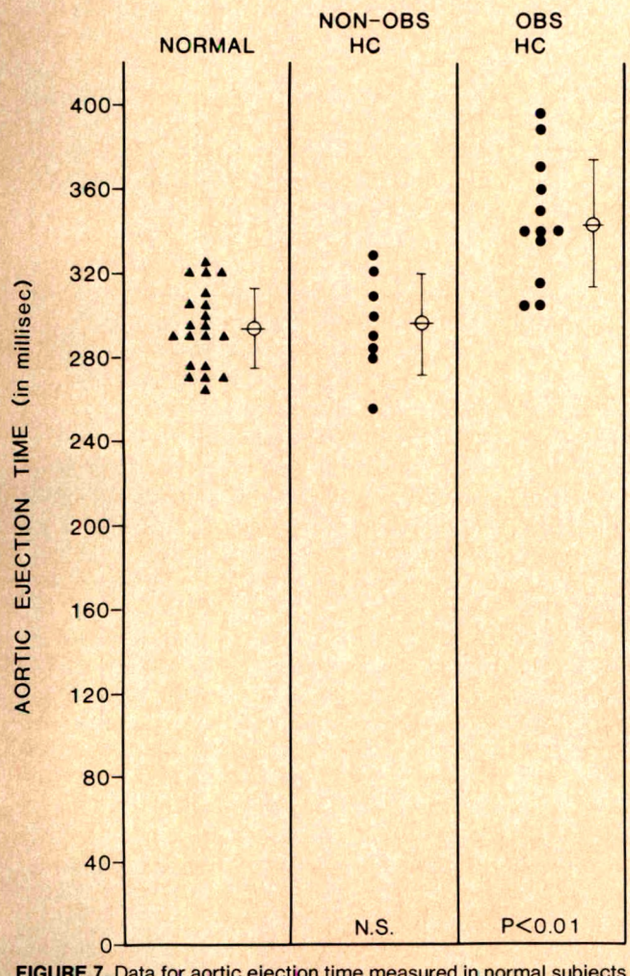

FIGURE 7. Data for aortic ejection time measured in normal subjects and patients with nonobstructed (NON-OBS) and obstructed (OBS) hypertrophic cardiomyopathy (HC). In the patients with obstructed HC, ejection time measurements were plotted from the Doppler aortic flow tracings in 9 patients and from the aortic valve echogram in 3.

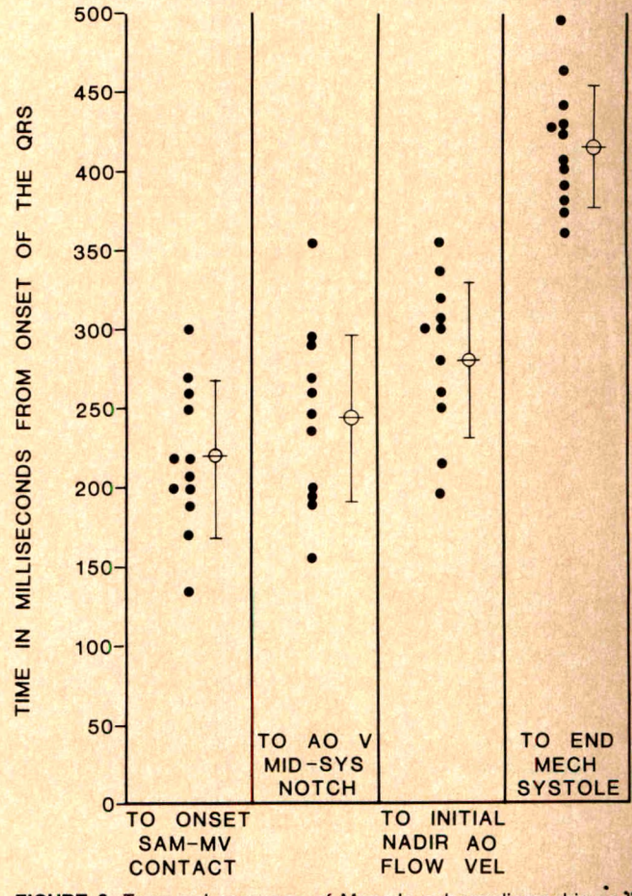

FIGURE 8. Temporal sequence of M-mode echocardiographic and Doppler aortic flow velocity events in patients with obstructive hypertrophic cardiomyopathy. The 4 panels show data for the time from onset of QRS complex to the onset of mitral valve-septal contact (SAM–MV), aortic valve partial midsystolic closure (maximal) (AO V MID-SYS NOTCH), midsystolic nadir on the Doppler aortic flow velocity (AO FLOW VEL curve), and end of ejection (END MECH SYSTOLE). Data in the middle 2 panels is plotted for only the 11 patients who had partial midsystolic closure on the aortic valve echogram and a midsystolic rapid deceleration in the aortic flow velocity.

echogram are nearly simultaneous events. The time from onset of QRS to the midsystolic nadir on the Doppler aortic flow velocity curve averaged 284 ms (range 195 to 355) which was an average of 40 ms after midsystolic partial closure on the aortic valve echogram and 66 ms after the onset of mitral valve–septal contact. The time from onset of QRS to end of ejection averaged 417 ms (range 360 to 495). Thus, the time from onset of QRS to onset of mitral valve–septal contact, aortic valve midsystolic partial closure, and midsystolic flow velocity nadir all averaged between one-half and two-thirds of the time of total electromechanical systole.

Left atrial flow velocity recording: Doppler flow velocity tracings were recorded in the left atrium in 5 patients with obstructed and 6 patients with nonobstructed HC. Four of 5 patients with obstructed HC, but none of 6 patients with nonobstructed HC, had mitral regurgitation. Figure 6 (bottom) is a left atrial flow velocity recording from patient 12, who had obstructed HC. Diastolic flow above the 0 line represents blood flow in the normal direction from left atrium to left ventricle; turbulent systolic flow above and below this line represents regurgitant flow into the left atrium. Mitral regurgitation (intensity of turbulence) is most prominent after the time of septal–mitral valve contact.

Summary of temporal sequence in obstructed hypertrophic cardiomyopathy: Figure 6 shows the sequence of events in a patient with obstructed HC. All 3 records, from the same patient, were matched such that the preceding RR intervals for each beat were within 20 ms of each other. The onset of LV posterior wall motion and the onset of aortic ejection were initial and near-simultaneous events. The next event was the attainment of peak aortic flow velocity, followed by the onset of mitral valve–septal contact and turbulent flow in the left atrium, and the rapid deceleration of aortic blood flow velocity in midsystole. Mitral regurgitation is recorded until just before the end of mitral valve–septal contact.

Discussion

Our echo Doppler studies demonstrate several differences between patients with obstructed HC and those with nonobstructed HC. First, although Doppler ascending aortic flow velocity patterns in patients with nonobstructed HC and normal subjects were similar, patterns in patients with obstructed HC differed from those in normal subjects and patients with nonobstructed HC. Specifically, the abnormal flow pattern, seen in 11 of 12 patients with obstructed HC, consisted of a rapid decrease in aortic flow velocity in midsystole, and was not seen in any of the patients with nonobstructed HC or normal subjects. Quantitatively, the patients with obstructed HC had a higher mean ejection time (345 ms) than those with nonobstructed HC (296 ms, $p < 0.02$) or normal subjects (294 ms, $p < 0.01$). Furthermore, the deceleration time index (i.e., the time from peak to 75% of peak flow velocity) was significantly shorter in patients with obstructed HC than in those with nonobstructed HC or normal subjects ($p < 0.001$).

The abnormal pattern of aortic blood flow velocity in patients with obstructed HC was first described by Hernandez et al,[3] who used intraaortic pressure gradient recordings. They noted that peak velocity occurred in early systole and was followed by an abrupt decrease in flow velocity at midsystole, with a diminished late systolic velocity. Other investigators, using electromagnetic flowmeters in patients with obstructed HC, have reported similar findings in the aorta[5] and brachial artery.[6]

Joyner et al[15] used continuous-wave Doppler to record phasic carotid artery flow transcutaneously in 12 patients with obstructed HC. All of their patients showed a rapid rise to a peak in early systole, an abrupt decrease in carotid flow velocity in midsystole and a slow late systolic flow wave. Boughner et al[16] used a continuous-wave Doppler transducer in the suprasternal notch to record flow velocity in the aortic arch in 3 patients with HC.[16] In 1 patient with a LV outflow gradient at rest, the aortic flow velocity pattern was characterized by a sharp early peak followed by a rapid decrease in velocity in midsystole, and a second lower peak in late systole. In 2 patients with HC without an LV outflow gradient, a normal aortic flow velocity tracing was noted.

As in these studies, we also found, in the patients with obstructed HC, an initial peak in flow velocity followed by a fall in midsystole to a lower velocity in late systole and in our patients with nonobstructed HC, a normal flow velocity pattern. The early reduction of ascending aortic blood flow velocity in the patients with obstructed HC does not appear to be merely a result of early completion of mechanical systole by a hyperdynamic left ventricle. This conclusion is supported by several observations. First, ejection time as measured by 2 independent methods (Doppler aortic flow velocity curves and aortic valve echograms) was longer in patients with obstructed HC than in those with nonobstructed HC or normal subjects. Second, LV minor-axis shortening on M-mode echo continued after both the initial mitral valve–septal contact and the midsystolic nadir of aortic blood flow velocity. Third, analysis of left atrial flow velocity recordings indicated that early deceleration of aortic blood flow velocity in midsystole appears to be a result of SAM of the mitral valve, which also results in mitral regurgitation.[17,18] Wigle et al[17] found that all 33 of their patients with HC and LV outflow gradients had evidence of mitral regurgitation by indicator-dilution techniques.[17]

Our findings differ from those recently reported by Murgo et al.[2] They studied 30 patients with HC and 29 patients with no evidence of cardiovascular disease. LV angiograms were recorded in all patients. A multisensor catheter was used to determine ascending aortic flow velocity electromagnetically as well as high-fidelity LV and aortic pressures. The 30 patients with HC included 9 with intraventricular pressure gradients at rest, 12 with pressure gradients only with provocation, and 9 with no pressure gradients despite provocation. These investigators found no significant differences between any of the 3 HC subgroups in either aortic ejection time or the time during which forward aortic flow occurred as a percentage of total systolic ejection period. They concluded that outflow obstruction, as traditionally defined by the presence of an abnormal intraventricular

pressure gradient and systolic anterior motion of the mitral valve, does not impede LV outflow in HC.

Although Murgo et al concluded that LV ejection times were not different in patients with obstructed HC, those with nonobstructed HC and normal subjects, their actual mean values for ejection times were similar to our measurements. In their study, systolic ejection times, measured from electromagnetic flow analysis, averaged 322 ± 32 ms in the group with LV gradients, 292 ± 28 ms in the group without gradients, and 286 ± 32 ms in normal subjects. Ejection times in our study averaged 345 ± 30 ms in the group with obstructed HC, 296 ± 24 ms in the group with nonobstructed HC and 294 ± 19 ms in normal subjects. When Murgo et al measured ejection times using frame-by-frame analysis of LV angiograms, they found a highly significant difference ($p < 0.001$) between values in HC patients with gradients (356 ± 53 ms), and both HC patients without gradients (303 ± 13 ms) and normal subjects (278 ± 36 ms). Two other studies have found ejection time to be significantly greater than normal in patients with HC and LV outflow gradients.[4,19]

There are several possible explanations for the different conclusions reached by us and Murgo et al. First, not all patients with HC in our study underwent cardiac catheterization. However, all had asymmetric septal hypertrophy (septal–free wall ratio of 1.7 or greater and an absolute septal thickness of at least 19 mm), as well as echo evidence suggesting an LV outflow tract pressure gradient of 45 mm Hg or greater (using the obstruction index of Pollick et al[10]). In view of the published experience showing a good correlation between echo and angiographic observations in HC, the lack of catheterization data in every patient in the present study probably does not account for the differences between the 2 studies. Moreover, 7 of the 8 patients with nonobstructed HC in the current study had either a positive family history or catheterization confirmation of the disease. A second difference between the 2 studies is that Murgo et al used angiographic and electromagnetic flow measurements to estimate ejection time, whereas we used measurements from the Doppler flow tracings and aortic valve echograms. Also, conclusions about LV shortening were made from angiographic measurements in their study, whereas our conclusions are based on dimensional changes measured from echocardiograms.

It is important to consider 2 factors that theoretically may have played a role in the longer mean ejection time in the patients with obstructed HC compared with values in patients with nonobstructed HC and normal subjects. First, both the patients with obstructed and nonobstructed HC were older (mean 39 to 43 years, respectively) than the 20 normal subjects (mean age 28 years). However, in a recent preliminary report, age had no effect on the aortic ejection time measured from Doppler aortic flow velocity tracings in 95 subjects without evidence of cardiovascular disease.[20] Second, the fact that 11 of the 12 patients with obstructed HC were taking propranolol, whereas only 2 of the 8 patients with nonobstructed HC were taking this drug, may have resulted in the longer mean ejection time in the patients with obstructed HC. However, heart rates were not significantly different between patients with obstructed HC (mean 64 ± 10 beats/min) and those with nonobstructed HC (58 ± 9 beats/min). Furthermore, no patient taking propranolol had evidence of a subnormal LV ejection fraction by echo or LV angiography. Consequently, although propranolol treatment may have had some effect, it is unlikely that it was responsible for the significant differences in ejection time between our patients with obstructed HC and those with and nonobstructed HC.

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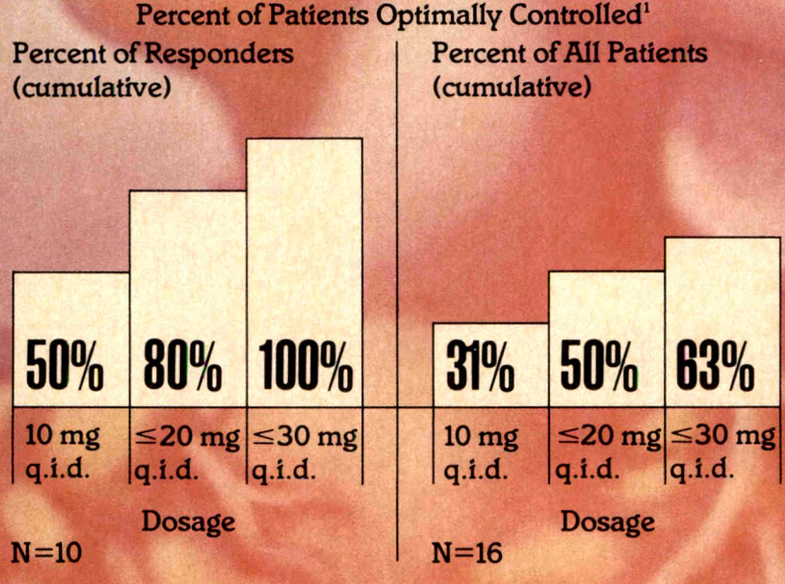

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Contraindications: Hypersensitivity or idiosyncrasy to this drug or other nitrates or nitrites.
Warnings: Benefits of use during the early days of an acute myocardial infarction have not been established; if used in early infarction, hemodynamic monitoring and frequent clinical assessment should be made because of the potential deleterious effects of hypotension.
Precautions: *General.* Severe hypotensive response, particularly with upright posture, may occur even with small doses; therefore use caution in subjects with blood volume depletion from diuretic therapy or with low systolic blood pressure (eg, below 90 mm Hg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrates may aggravate angina caused by hypertrophic cardiomyopathy. Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination; dose adjustment of either class of agents may be necessary. There are reports of anginal attacks being more easily provoked and of rebound in hemodynamic effects soon after nitrate withdrawal; when therapy is being terminated, withdraw the drug gradually rather than stopping it abruptly.
Information for Patients. Headache may occur during initial therapy; it is usually relieved by standard headache remedies, or by lowering the dose, and tends to disappear after the first week or two of use.
Drug Interactions. Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates. Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect, depending on the agent.
Carcinogenesis, Mutagenesis, Impairment of Fertility. No long-term studies in animals have been performed.
Pregnancy Category C. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers. It is not known whether this drug is excreted in human milk; because many drugs are excreted in human milk, caution should be exercised in nursing women.
Pediatric Use. Safety and effectiveness in children have not been established.
Adverse Reactions: Adverse reactions, particularly headache and hypotension, are dose related. At various doses, the following have been observed:
Headache is the most common (average occurrence about 25%) and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon.
Overdosage: *Treatment.* Prompt removal of the ingested material by gastric lavage is reasonable but not documented to be useful. Keep the patient recumbent in a shock position and comfortably warm. Passive movements of the extremities may aid venous return. Administer oxygen and artificial respiration if necessary. If methemoglobinemia is present, administer methylene blue (1% solution), 1 to 2 mg/kg intravenously. *WARNING:* Epinephrine is ineffective in reversing the severe hypotensive events associated with overdose. It and related compounds are contraindicated in this situation.
Consult direction circular before prescribing.

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THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC
Henry N. Neufeld, MD, FACC
1978, 288 PAGES, 110 ILLUS., 1,000 REF.

Every Cardiologist, Internist, Pediatrician, Surgeon — Indeed, *Every Physician* — Should Have a Good Basic Knowledge of The Pre-excitation Syndrome. Here Are Just a Few Reasons Why This is so Essential:

- ⅓ of all pre-excitation cases are misdiagnosed.
- 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies on patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals

The 13 Chapters Are a Comprehensive Summary

1. General Considerations
2. The Electrocardiogram in the Pre-excitation Syndrome: Complexes and Configurations
3. The Electrocardiogram in the Pre-excitation Syndrome: Disturbances of Rate and Rhythm
4. Pathology
5. Noninvasive Methods of Investigation
6. Invasive Methods of Investigation
7. Prognosis
8. Treatment
9. Problems of Diagnosis — Some Illustrative Cases
10. Summary of Findings and Theories of Pre-excitation Syndrome
11. Concept of Interacting Structural and Functional Factors
12. Explanation of Some Phenomena of the Pre-excitation Syndrome by the Proposed Concept
13. Various QRS Patterns in the Different Forms of Pre-excitation

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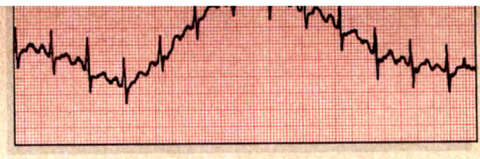

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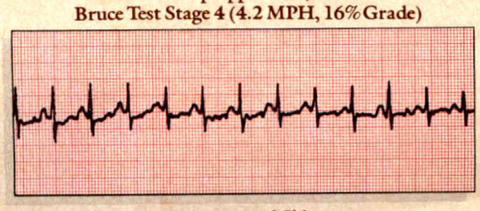

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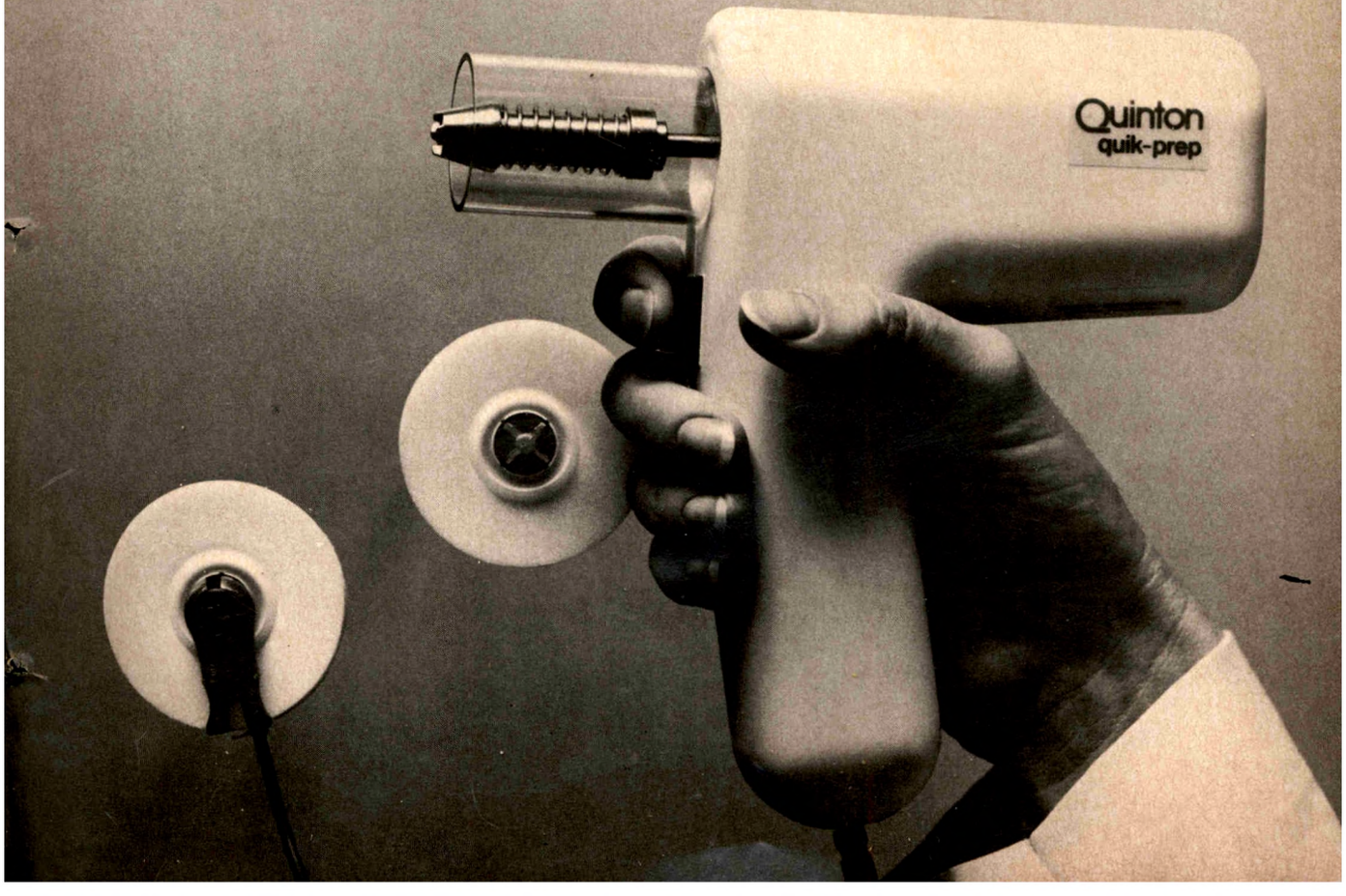

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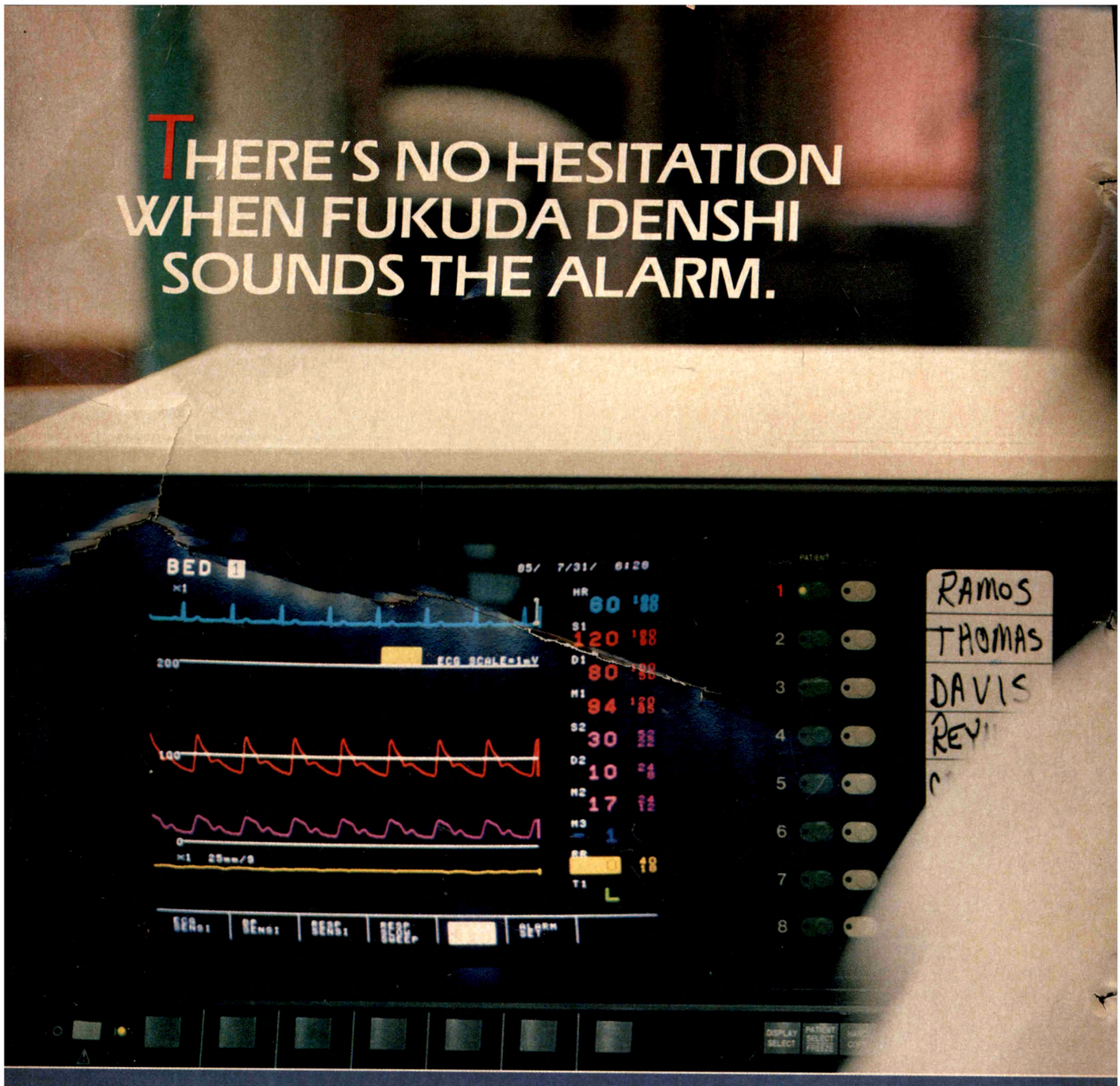

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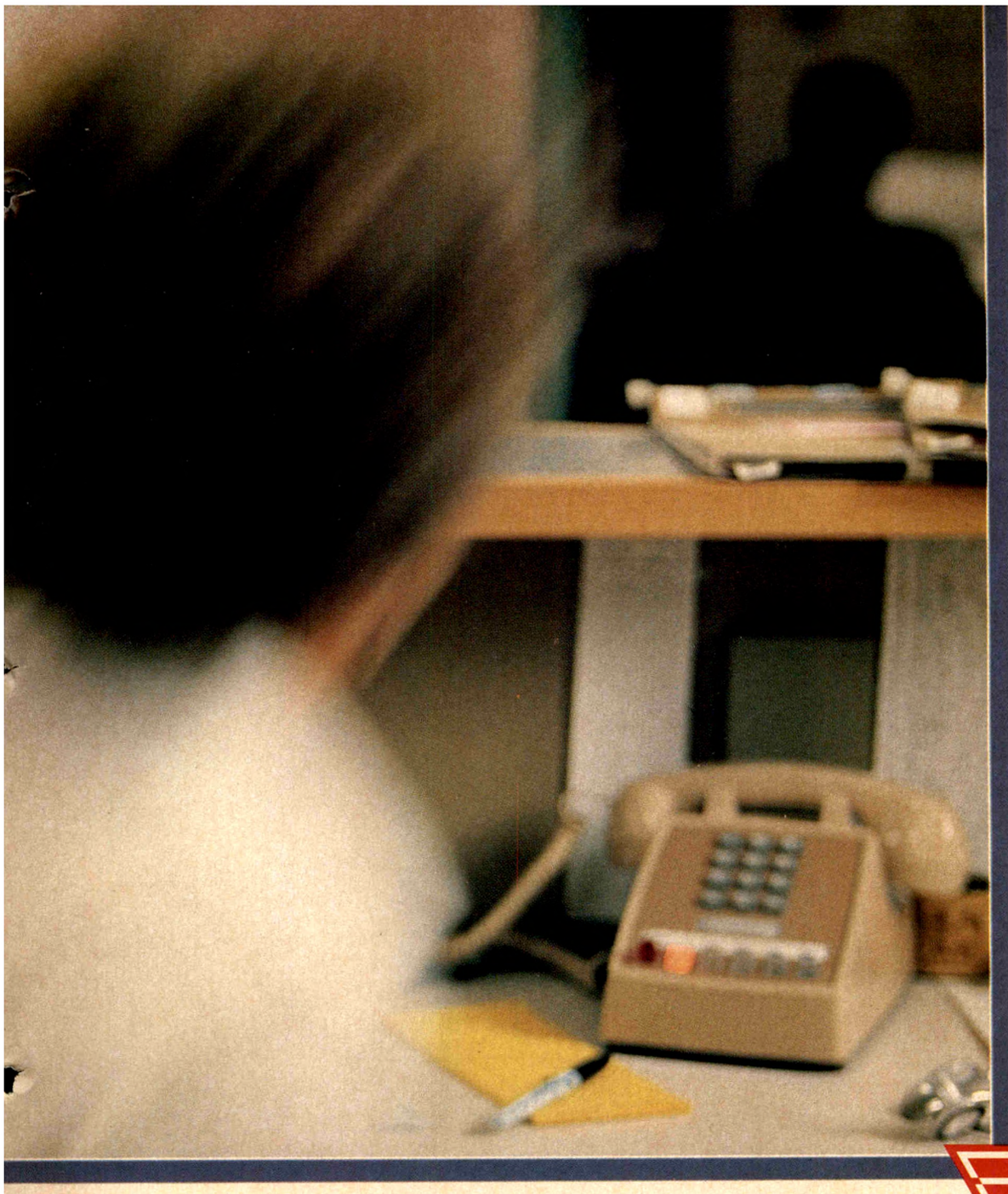

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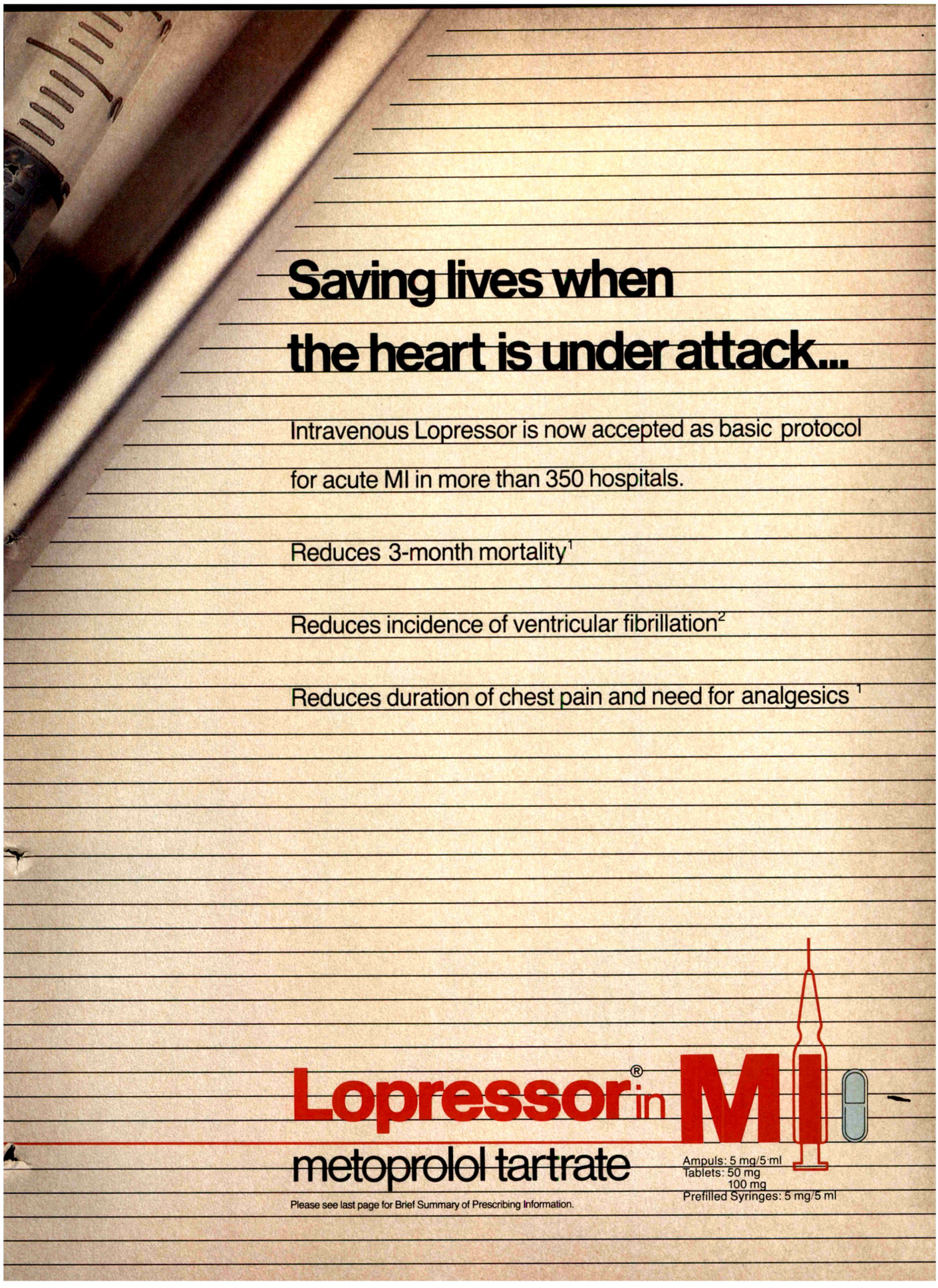

Saving lives when the heart is under attack...

Intravenous Lopressor is now accepted as basic protocol for acute MI in more than 350 hospitals.

Reduces 3-month mortality[1]

Reduces incidence of ventricular fibrillation[2]

Reduces duration of chest pain and need for analgesics[1]

Lopressor®in MI

metoprolol tartrate

Ampuls: 5 mg/5 ml
Tablets: 50 mg
100 mg
Prefilled Syringes: 5 mg/5 ml

Please see last page for Brief Summary of Prescribing Information.

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...and protecting healing hearts in the months ahead

The combination of early intravenous administration of Lopressor followed by long-term oral therapy resulted in a 36% reduction of three-month mortality in patients with definite or suspected acute MI in the Göteborg Trial.[1]

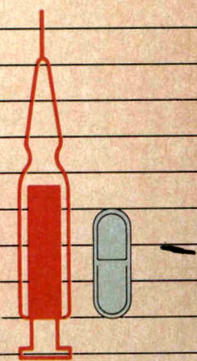
Alternatively, oral treatment can begin within 3 to 10 days of the acute event.

Treatment should be continued for 1-3 years.

Lopressor is contraindicated in patients with a heart rate <45 beats/min; significant heart block greater than first degree (P-R interval ≥0.24 sec); systolic blood pressure <100 mmHg; or moderate-to-severe cardiac failure. Please see last page for Brief Summary of Prescribing Information.

1. Hjalmarson Å, et al: The Göteborg Metoprolol Trial: Effects on mortality and morbidity in acute myocardial infarction. *Circulation* 1983 (June); 67(suppl 1):I-26-I-32.

2. Rydén L, et al: A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrhythmias. *N Engl J Med* 1983 (Mar 17); 614-617.



Lopressor® in **MI**

metoprolol tartrate

Ampuls: 5 mg/5 ml
Tablets: 50 mg
100 mg
Prefilled Syringes: 5 mg/5 ml

Changing the Course of Cardiovascular Care

Saving lives when the heart is under attack

...and protecting healing hearts in the months ahead

Lopressor®
metoprolol tartrate

Tablets
Ampuls
Prefilled Syringes

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Myocardial Infarction
Lopressor ampuls, prefilled syringes and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; significant heart block greater than first degree (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent $beta_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a $beta_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and $beta_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness. Patients should contact the physician if any difficulty in breathing occurs, and before surgery of any type, the patient should inform the physician or dentist that he or she is taking Lopressor.

Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a 1-year study in dogs, there was no evidence of drug-induced toxicity at or below oral dosages of 105 mg/kg per day. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

Pregnancy Category B
Reproduction studies have been performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg and have revealed no evidence of impaired fertility or teratogenicity due to Lopressor. Increased postimplantation loss and decreased neonatal survival did occur in the rats (threshold between 50 and 500 mg/kg), and distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

C84-38 (Rev. 7/85)

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Primary Acute Pericardial Disease: A Prospective Series of 231 Consecutive Patients

G. PERMANYER-MIRALDA, MD, J. SAGRISTÁ-SAULEDA, MD, and J. SOLER-SOLER, MD

A series of 231 patients with "primary" acute pericardial disease (acute pericarditis or tamponade presenting without an apparent cause) were studied according to the following protocol: general clinical and laboratory studies (stage I), pericardiocentesis (stage II), pericardial biopsy (stage III) and blind antituberculous therapy (stage IV). In 32 patients (14%) a specific etiologic diagnosis was obtained (13 with neoplasia, 9 with tuberculosis, 4 with collagen vascular disease, 2 with toxoplasmosis, 2 with purulent pericarditis and 2 with viral pericarditis). "Diagnostic" pericardiocentesis (32 patients) was performed when clinical activity and effusion persisted for longer than 1 week or when purulent pericarditis was suspected, whereas "therapeutic" pericardiocentesis (44 patients) was performed to treat tamponade; their diagnostic yield was 6% and 29%, respectively. "Diagnostic" biopsy (20 patients) was carried out when illness persisted for longer than 3 weeks, whereas "therapeutic" biopsy was performed whenever pericardiocentesis failed to relieve tamponade; their diagnostic yield was 5% and 54%, respectively. The diagnostic yield difference between "diagnostic" and "therapeutic" procedures was significant ($p < 0.001$); in contrast, the global diagnostic yield of pericardiocentesis (19%) and biopsy (22%) was similar. At the end of follow-up (1 to 76 months, mean 31 ± 20), no patient in whom a diagnosis of idiopathic pericarditis had been made showed signs of pericardial disease. It is concluded that a "diagnostic" procedure is not warranted as a routine method, a choice between "therapeutic" pericardiocentesis and biopsy is circumstantial and must be individualized, and only through a systematic approach can a substantial diagnostic yield be reached in primary acute pericardial disease.

(Am J Cardiol 1985;56:623–630)

Clinical and pathologic features of acute pericardial disease have been known for many years.[1–3] By contrast, the approach to the etiologic diagnosis in several pericardial syndromes is not well established. The most frequently disquieting dilemma for the clinical cardiologist is the patient with acute pericardial disease without an apparent cause (primary acute pericardial disease). Most patients have self-limited clinical features and do not constitute a major problem of management, despite an unrecognized cause in most cases; however, in many patients the illness is not self-limited, and in many of such patients even an extensive workup is likely to result in negative etiologic conclusions. The possibility of life-threatening, treatable disease makes etiologic diagnosis a very important issue. In particular, tuberculous pericarditis is sometimes a very difficult diagnosis, and its early identification is necessary for successful treatment. This situation may easily lead to a useless, long-term antituberculous therapy; it is made worse by the controversial indications[4,5] for pericardiocentesis and open pericardial drainage with biopsy. Dispute has mainly been based on the risk and therapeutic value of closed needle pericardiocentesis compared with surgical drainage, with less emphasis on the diagnostic capabilities of both procedures. General agreement as to the safest and most sensitive approach to the etiologic diagnosis of acute pericardial disease is not found in published reports; in fact, attempts to analyze this common clinical problem are surprisingly scarce.[6] We believe that some clarification can be provided by the prospective application of a systematic study in a large group of patients with primary acute pericarditis and cardiac tamponade.

From the Servicio de Cardiologia, Departamento de Medicina, Ciudad Sanitaria "Vall d'Hebron", Barcelona, Spain. Manuscript received February 14, 1985; revised manuscript received May 13, 1985, accepted May 15, 1985.

Address for reprints: G. Permanyer-Miralda, MD, Servicio de Cardiologia, Ciudad Sanitaria "Vall d'Hebron", Paseo Valle de Hebron, s/n 08035 Barcelona, Spain.

Methods

The present study is composed of 231 consecutive patients (176 males, 55 females, aged 8 to 85 years, mean 41) who were

TABLE I Stage I: Diagnostic Yield

Type Pericarditis	No.
Tuberculous	4
Viral	2
Rheumatic	2
Toxoplasmic	2
Collagen vascular—disease	2*
Neoplastic (lymphoma)	1
Total	13

* Systemic lupus erythematosus (1 case); hypereosinophilic syndrome associated to Churg-Strauss vasculitis (1 case).

admitted to the Cardiology Service from January 1977 to October 1983 with acute pericarditis or cardiac tamponade or both. Patients with postinfarction or postpericardiotomy syndromes, chronic pericardial effusion or chronic constrictive pericarditis were not included in the study. Patients with pericarditis associated with renal failure, known neoplastic disease, trauma or radiation were not included. Acute pericarditis was diagnosed when at least 2 of the following criteria were present: characteristic chest pain, pericardial friction rub, and serial repolarization changes on the electrocardiogram. Cardiac tamponade was diagnosed when there were clinical signs of venous hypertension or paradoxical pulse (inspiratory decrease of arterial pressure >10 mm Hg)[7] associated with echocardiographic evidence of pericardial effusion in the absence of any other form of heart disease.

Study protocol: All patients were prospectively studied according to the following study protocol (Fig. 1).

Stage I—general studies and echocardiogram: In this stage, the following studies were carried out: complete clinical history, physical examination, electrocardiography, chest x-ray film, rheumatoid factor, specific serologic test for toxoplasmosis (immunofluorescent antibodies), tuberculin skin test (purified protein derivative 10 μ) and virologic studies (viral cultures in pharyngeal swabs and feces). In patients with tamponade, suspicion of pericardial effusion or illness lasting for more than 1 week, the following investigations were performed: echocardiography, tubercle bacilli investigation in 3 samples of sputum or gastric aspirate, blood culture, agglutinin titer against *Brucella melitensis*, and antinuclear antibody determination. In addition, any other routine study suggested by the initial examination was performed.

Stage II—pericardiocentesis: Pericardiocentesis was performed under the following circumstances: (1) cardiac tamponade, (2) clinical suspicion of purulent pericarditis, and (3) illness lasting for more than 1 week, with echocardiographic evidence of anterior and posterior pericardial effusion. In this study, pericardiocentesis was considered "therapeutic" if it was performed after the first indication; it was considered "diagnostic" if it was performed for the other 2 indications.

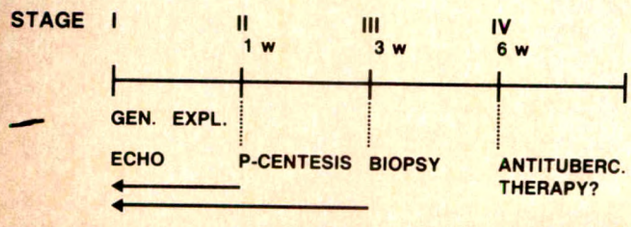

FIGURE 1. Study protocol. The protocol consists of 4 stages at different intervals. "Diagnostic" pericardiocentesis (P-CENTESIS) and biopsy are scheduled at 1 and 3 weeks (w), respectively, after hospital admission. "Therapeutic" procedures can be carried out at any time of the clinical evolution (**arrows**).

Pericardiocentesis was carried out either through subxiphoid or intercostal approaches. The following studies were carried out in the pericardial fluid: packed red cell volume, total proteins, lactic acid dehydrogenase, culture in ordinary and Löwenstein media, viral studies (culture in cellular lines HEP 2 and VERO, and in fibroblasts of human embryo lung), direct search for tubercle bacilli (Ziehl-Nielsen stain) and cytologic examination. When quickly relapsing or grossly hemorrhagic pericardial effusion was observed, the appropriate studies to rule out neoplastic disease were instituted.

Stage III—surgical biopsy of the pericardium: Pericardial biopsy was performed under 2 circumstances: (1) as a part of a therapeutic procedure (surgical drainage) in patients with severe tamponade relapsing after pericardiocentesis ("therapeutic" biopsy), and as a diagnostic procedure ("diagnostic" biopsy) in patients with an illness more than 3 weeks in duration after hospital admission and without etiologic diagnosis having been reached by previous procedures. Pericardial biopsy was performed after 1 week of treatment with isoniazide (400 mg/day) and streptomycin (1 g/day); this treatment was discontinued 1 week after biopsy unless tuberculosis was demonstrated. Biopsy was carried out by the subxiphoid approach. Histologic and bacteriologic study of the biopsy specimen and study of the pericardial fluid (as previously described) were performed. Other studies to rule out neoplasia were also done.

Stage IV: If fever and pericardial effusion of unknown origin persisted for more than 5 to 6 weeks, and did not lead to tamponade or constriction, blind antituberculous treatment was considered.

Pericardiectomy: Pericardiectomy was performed under the following circumstances: evolution to constrictive pericarditis, persistence of tamponade after surgical drainage, and relapsing pericarditis with frequent and disabling episodes.

Treatment: Patients were treated only with bedrest and nonsteroidal antiinflammatory drugs unless a specific cause was found.

Follow-up: Patients were seen in the outpatient clinic at 3 months, 6 months, 1, 2 and 5 years after hospital discharge, or more often as indicated by clinical evolution. After 5 years, follow-up was interrupted in patients with normal findings.

Results

Stage I: Pericardial effusion was present by classic echocardiographic criteria[8] in 124 of 231 patients (54%). The diagnostic yield of this stage is listed in Table I. Tubercle bacilli were found in sputum (culture in Löwenstein medium) in 4 patients. In 2 of the 33 unselected patients in whom viral cultures were performed, Coxsackie B virus was isolated from pharyngeal swabs and feces. In 110 unselected patients, serologic studies for toxoplasmosis were performed; 2 patients had a characteristic immunofluorescent antibody curve or positive IgM antibody, which allowed a diagnosis of active toxoplasmosis; in the other 10 patients, an immunofluorescent antibody titer (100 IU or higher) was found, but no serial studies or search for IgM antibodies were performed, and therefore the diagnosis of active toxoplasmosis is doubtful. These 10 patients have been included in the group with acute idiopathic pericarditis.

Stage II: Eighty pericardiocenteses were performed in 76 patients (Table II). In 9 patients (12%), pericardiocentesis was unproductive; only 1 major complication was observed (hemopericardium secondary to right

TABLE II Pericardiocentesis: Diagnostic Yield

	No. of Pts	Nonprod.	+	0	Sen.	Spec.
"Diagnostic"	32 (42%)	9	2 (6%)	20 + 1*	...	...
"Therapeutic"	44 (58%)	0	13 (29%)†	28 + 3*	...	...
Total	76 (100%)	9	15 (19%)	48 + 4*	79%	98%

* False negative.
† One patient in this group corresponds to a patient with tubercle bacilli in Löwenstein medium, in whom a diagnosis of neoplasia had been made in the cytologic examination of the pericardial fluid (flase positive for specificity calculations).
Nonprod = nonproductive pericardiocentesis; Sen. = sensitivity; Spec. = specificity; + = positive diagnostic data; 0 = negative diagnostic data.

TABLE III Stage II: Diagnostic Yield

Type Pericarditis	No.
Neoplastic	9
Tuberculous	3
Purulent	2
Collagen vascular disease	1
Total	15
False positive	1
False negative	4

TABLE IV Global Diagnostic Yield

	No. of Pts	Diagnoses	New Diagnoses
Stage I	231	13	13
Stage II	76	15	13
Stage III	31	7	1
Stage IV	0	0	0
Pericardiectomy	15	6	2
Other procedures	...	...	3
Total			32

ventricular laceration, needing surgical treatment with uneventful recovery).

"Diagnostic" pericardiocentesis was performed in 32 patients (in 31 for illness longer than 1 week and in 1 for suspicion of purulent pericarditis). In 2 patients, positive diagnostic data were obtained: positive culture for tubercle bacilli and purulent exudate, respectively. The only false-negative diagnosis corresponded to a patient in whom lymph node biopsy specimen and subsequent pericardiectomy revealed tuberculosis.

"Therapeutic" pericardiocentesis was performed in 44 patients. Diagnostic data were obtained in 13 patients: neoplastic cells (9 cases), positive culture for tubercle bacilli (2 cases), purulent exudate (1 case), and hypereosinophilic exudate (1 case). Three of the 31 negative results were false-negative; in subsequent studies they were shown to correspond to tuberculous pericarditis (1 case) and neoplastic pericarditis (2 cases: cardiac angiosarcoma and metastasic carcinoma, respectively). One patient had a positive culture for tubercle bacilli, but a diagnosis of neoplasia had been made in the cytologic examination of the effusion; this latter finding is considered to be a false-positive diagnosis for purposes of specificity calculation.

In this stage, an etiologic diagnosis could be established in 15 patients (Table III), although in 2 of them (1 with hypereosinophilic syndrome and 1 with lymphoma) it had been already made in stage I; consequently, in stage II 13 new true-positive diagnoses were made (Table IV). On the other hand, there were 4 false-negative diagnoses (2 patients with tuberculous and 2 with neoplastic pericarditis) and 1 false-positive diagnosis (neoplastic pericarditis being diagnosed by cytologic examination in a patient with tuberculous pericarditis). Sensitivity and specificity of pericardiocentesis were 79% and 98%, respectively.

The global diagnostic yield of pericardiocentesis was 19% (15 of 76 patients) (Fig. 2); however, "diagnostic" pericardiocentesis had only a diagnostic yield of 6% (2 patients), whereas the diagnostic yield of "therapeutic" pericardiocentesis was 29% (13 patients).

Stage III: Surgical pericardial drainage with biopsy was carried out in 31 patients (Table V). No complications were observed.

"Diagnostic" biopsy (20 patients): The only positive result (5%) was in a case of tuberculous pericarditis. One false-positive result was observed in a patient whose biopsy specimen was interpreted as metastatic adenocarcinoma, and who remained symptom-free and without evidence of pericardial disease or neoplasia 4 years afterward. One false-negative result was observed in a patient with gastric carcinoma.

"Therapeutic" biopsy (11 patients): "Therapeutic" biopsy yielded 6 positive diagnoses (54%): neoplastic

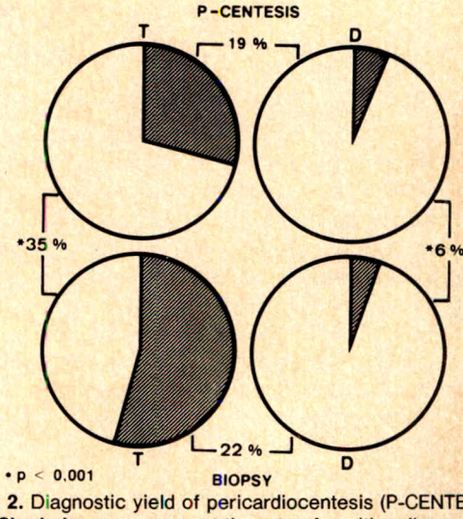

FIGURE 2. Diagnostic yield of pericardiocentesis (P-CENTESIS) and biopsy. **Shaded areas** represent the rate of positive diagnostic data. Although the diagnostic yield of pericardiocentesis and biopsy are similar (19% and 22%, respectively), there is a significant difference ($p < 0.001$) when "therapeutic" (T) and "diagnostic" (D) procedures are compared (35% and 6%, respectively).

TABLE V Biopsy: Diagnostic Yield

	No. of Pts	+	0	Sens.	Spec.
"Diagnostic"	20 (65%)	1 (5%) + 1*	17 + 1†	...	...
"Therapeutic"	11 (35%)	6 (54%)	3 + 1† + 1‡	...	...
Total	31 (100%)	7 (22%) + 1*	20 + 2† + 1‡	78%	95%

* False positive.
† False negative.
‡ Inadequate specimen.
Sens. = sensitivity; Spec. = specificity; + = positive diagnostic data; 0 = negative diagnostic data.

TABLE VI Stage III: Diagnostic Yield

Type Pericarditis	No.
Neoplastic	3
Tuberculous	2
Purulent	2
Total	7
False positive	1
False negative	2

TABLE VII Pericardiectomy

Type Pericarditis	No.
Tuberculous	3
Neoplastic	2
Purulent	1
Total	6
False positive	1
False negative	1

pericarditis (3 cases), purulent pericarditis (2 cases) and tuberculous pericarditis (1 case). A false-negative result was observed in 1 patient with cardiac angiosarcoma in whom diagnosis was made in a subsequent pericardiectomy.

On the whole, 7 true-positive diagnoses (Table VI) were made in stage III, but only 1 was a new diagnosis (Table IV). Sensitivity and specificity of pericardial biopsy were 78% and 95%, respectively. The global diagnostic yield of pericardial biopsy was 22% (7 of 31 patients); however, the yield of "therapeutic" biopsy was 54% and of "diagnostic" biopsy only 5% (Fig. 2).

The global diagnostic yield (Fig. 2) of "therapeutic" procedures (pericardiocentesis and biopsy) was 35% (19 true-positive diagnoses in 55 procedures), whereas diagnostic yield of "diagnostic" procedures was 6% (3 true-positive diagnoses in 52 procedures). The difference between both rates is statistically significant ($p < 0.001$).

Stage IV: No patient reached stage IV. Accordingly, in no patient was blind antituberculous chemotherapy instituted.

Pericardiectomy: Pericardiectomy was performed in 15 patients (as a result of constrictive pericarditis in 9). Pericardiectomy resulted in diagnostic data in 6 patients (Table VII). In 2 patients the diagnosis had not been previously made (Table IV). There was 1 false-positive diagnosis (1 patient with a pathologic diagnosis of neoplasia in whom absolutely uneventful long-term follow-up led to the diagnosis of idiopathic pericarditis) and 1 false-negative diagnosis (purulent pericarditis).

Invasive extracardiac procedures: In 3 patients, etiologic diagnosis was made by means of the following studies (1 case each): lymph node biopsy (squamous carcinoma), pleural biopsy (tuberculosis) and gastrointestinal study with subsequent operation (gastric adenocarcinoma).

In the whole series of 231 patients, invasive cardiac procedures were carried out in 79 (34%) ("invasive" group). One hundred twenty-six invasive procedures were performed (80 pericardiocenteses, 31 biopsies and 15 pericardiectomies); these procedures resulted in an etiologic diagnosis in 20 patients (25%). The etiologic diagnoses after completion of the studies are listed in Table VIII. A definite diagnosis was made in 32 patients (14% of the whole series); in 16 of the 32 patients (50%), the diagnosis was made only by means of invasive cardiac procedures.

Relative prevalence of tamponade and pericardial effusion in the different etiologies: The relative prevalence of pericardial effusion and tamponade in the different etiologic types of pericarditis are listed in Table IX. Forty-four patients had tamponade. Of these, 28 patients (64%) had acute idiopathic pericarditis, 11 had neoplastic pericarditis, 3 had tuberculous pericarditis, 1 patient had purulent pericarditis and 1 had pericarditis associated with hypereosinophilic syndrome.

Follow-up: The follow-up period ranged from 1 to 76 months (mean 31 ± 20). Twenty-three patients (10%) were lost to follow-up; in 9 others follow-up was incomplete. Therefore, incomplete follow-up data are available for 32 patients (13%). However, only 3 of these 32 patients belonged to the group that was "invasively" studied (79 patients); in the remaining 29 patients the clinical symptoms and effusion, when present, resolved within a short time. This group had no finding that suggested a specific cause was present in the protocol study performed during admission.

Clinical course: Eight patients died during follow-up (all with neoplastic pericarditis). In 7 patients, a subacute evolution to a classic form of constrictive pericarditis requiring pericardiectomy was observed (4 with tuberculous pericarditis, 2 with purulent pericarditis and 1 with neoplastic pericarditis). Five other patients (3 with idiopathic pericarditis, 1 with tuberculous pericarditis and 1 with neoplastic pericarditis) developed effusive-constrictive pericarditis, and 2 of these (1 with tuberculous pericarditis and 1 with idiopathic pericarditis) required pericardiectomy. Therefore, in 203 patients with idiopathic, viral and toxoplasmic pericarditis, only 1 patient (with effusive-constrictive

TABLE VIII Etiologic Diagnosis

Acute idiopathic pericarditis		199
Neoplastic pericarditis		13
Carcinoma of lung	5	
Carcinoma of unknown origin	5	
Gastric carcinoma	1	
Lymphoma	1	
Cardiac angiosarcoma	1	
Tuberculous pericarditis		9
Purulent pericarditis		2
Toxoplasmic pericarditis		2
Viral pericarditis		2
Other causes		4
Rheumatic fever	2	
Churg-Strauss vasculitis	1	
Systemic lupus erythematosus	1	
Total		231

TABLE IX Prevalence of Effusion and Tamponade

	No. of Pts	Effusion	Tamponade
Neoplastic pericarditis	24	22	15 (68%)*
Tuberculous pericarditis	207	102	29 (28%)*
Purulent pericarditis			
Other causes			

* $p < 0.001$.
Percentages relative to patients with effusion.

pericarditis) required pericardiectomy, whereas 8 of the 24 patients with tuberculous, neoplastic and purulent pericarditis required it. In the last clinical examination none of the remaining patients with a diagnosis of acute idiopathic, viral or toxoplasmic pericarditis had died or had signs of constrictive pericarditis or another significant clinical condition.

Discussion

The problem of primary pericardial disease: Often, the etiologic diagnosis of pericardial disease is carried out according to the principle of "guilt by association."[9] This is the case when pericardial disease can be related to an associated condition, such as myocardial infarction, uremia or other known systemic disease. Even in these cases, the etiologic diagnosis may not be a straightforward matter. In addition, not infrequently the clinician is faced with the problem of recognizing severe, treatable disease in patients without noncardiac clues to the etiologic diagnosis. These instances may be labeled, on clinical grounds, primary pericardial disease. Frequently, the clinical features (acute onset with characteristic chest pain, absent or small effusion and quickly self-limited illness) are strongly indicative of acute idiopathic or viral pericarditis; not infrequently, however, idiopathic pericarditis shows less distinctive features, and its recognition from more severe and treatable conditions, such as tuberculosis or neoplasia, may be very difficult.[6,10,11] The occurrence of large or bloody effusions, cardiac tamponade or a clinical course over several weeks may make the etiologic diagnosis of pericarditis a difficult clinical dilemma, leading in some cases to the prescription of antituberculous therapy based on indirect diagnostic criteria.[12,13] Although considerable information about the usefulness of pericardiocentesis,[4–6,14] pericardial biopsy[4–6,13,15–18] or pericardiectomy[6,19] for etiologic diagnosis is available in published reports, comprehensive series on the value of an integrated approach to acute primary pericardial disease are lacking.

Limited etiologic value of clinical features: In the present series, clinical features of patients with tamponade or persisting effusion were of limited value for the etiologic diagnosis in the individual case. For instance, a long-standing, torpid clinical course has been considered suggestive of tuberculous pericarditis; however, in the present series, less than 2 weeks of evolution was present before admission in 4 of 9 patients. The presence of effusion, development of tamponade, hemopericardium and positive tuberculin skin test, although more common in some specific types of pericarditis, were prevalent enough in idiopathic cases to reduce their diagnostic usefulness in a particular patient. In fact, tamponade was relatively frequent (28%) in patients with acute idiopathic pericarditis with effusion, in contrast to previously reported data.[20] Moreover, the tuberculin skin test was not a reliable indicator of tuberculous pericarditis; in the present series it was negative in 3 of 9 patients with the latter condition, a similar prevalence as in the series of Fowler and Manitsas[17] but much lower than in the series by Rooney et al[13]; in contrast, it was positive in 41% of the tested patients with acute idiopathic pericarditis. However, grossly bloody pericardial effusion, although more frequent in neoplastic pericarditis (7 of 12 patients with effusion), was also seen in patients with acute idiopathic pericarditis, with a prevalence of 7 of 46 cases (in agreement with other series[6]). Even the combination of tamponade and hemopericardium was not by itself indicative of a particular cause; this combination was seen in 3 patients with acute idiopathic pericarditis.

Diagnostic yield of the present protocol: Thirty-two etiologic diagnoses (13%) were confirmed in the present series. This is not a strikingly low proportion considering the type of patients included in the present series. Regarding the methods that led to the etiologic diagnosis, these 32 patients are distributed as follows: (1) In 50% the cause was discovered only by invasive cardiac procedures (pericardiocentesis, pericardial biopsy or pericardiectomy). (2) In 37%, noncardiac studies disclosed the cause. (3) In 12%, the diagnosis was made both by noncardiac and invasive cardiac studies. The predominance of invasive diagnoses may be partially influenced by the failure to perform an objective diagnosis of viral or toxoplasmic pericarditis in cases in which this might have been done; however, our figures probably serve as an index of the proportion of diagnoses to be expected from cardiac and noncardiac studies as far as neoplastic, tuberculous and purulent pericarditis are concerned.

Diagnostic value of pericardiocentesis: Sensitivity and specificity of pericardiocentesis were high (79% and 98%, respectively), but diagnostic yield was markedly different, depending on whether pericardiocentesis was "diagnostic" (6%) or "therapeutic" (29%). The lower sensitivity of pericardiocentesis was related to its inability to demonstrate tuberculosis and neoplasia in 2 patients each. This shortcoming has been known for

many years.[6,10,17,21,22] The 9 patients with nonproductive pericardiocentesis did not bias the results in the "diagnostic" group, as only 1 of them (a patient with false-positive echocardiographic evidence of effusion) was discovered by subsequent studies to have neoplastic pericarditis, whereas the remaining 8 patients recovered uneventfully to the last follow-up control. In a similar way, hypothetical false-negative results seem to be virtually ruled out by subsequently adequate follow-up. In the case of tuberculous pericarditis (9 cases), pericardiocentesis did not prove very useful: In 2 of the 5 patients in whom it was performed, tubercle bacilli failed to be identified in pericardial fluid at all, whereas in the 3 patients from whom bacilli were recovered, identification was by growth in Löwenstein medium in all 3. Identification in all 5 was not by direct examination with the Ziehl-Nielsen stain, possibly because of a few bacilli in the fluid. This meant a delay of several weeks during which diagnosis was made by other procedures in 1 case. This limitation of pericardiocentesis in the diagnosis of tuberculous pericarditis has also been pointed previously.[11,13] In patients with neoplastic pericarditis, pericardiocentesis was more consistently useful than in tuberculosis, a diagnosis being obtained in 9 of 13 cases. However, pericardiocentesis failed to discover neoplastic cells in 2 patients; the occurrence of false-negative results in neoplastic pericarditis is well documented.[6,21,22]

Diagnostic value of pericardial biopsy: Pericardial biopsy as well as pericardiocentesis were of limited value in our patients in the absence of tamponade. The sensitivity and specificity of pericardial biopsy (78% and 95%, respectively) are almost the same as those of pericardiocentesis; similarly, its diagnostic yield was 5% (only 1 case) in "diagnostic" indications and 54% in "therapeutic" indications. Therefore, there appear to be good reasons for advising against biopsy, as well as against pericardiocentesis, when it is carried out only for diagnostic purposes. Limitations of pericardial biopsy lie mainly in its lower sensitivity in diseases with patchy pericardial involvement (especially neoplastic pericarditis,[6,23,24] where biopsy specimens in our series were negative in 2 of 6 patients) and in the possibility of false-positive diagnoses of neoplasia in cases of mesothelial hyperplasia.[25] Moreover, in all 5 cases of tuberculous pericarditis in which the pericardium was histologically examined either by biopsy or by pericardiectomy, the diagnosis was confirmed.

Diagnostic and therapeutic procedures: A striking result in our series is the very low rate of diagnoses made by "diagnostic" procedures (6%) compared with "therapeutic" procedures in which etiologic data were obtained in 35% of patients (Fig. 2). Accordingly, the distinction between "diagnostic" and "therapeutic" procedures is meaningful for clinical purposes. We believe that the major reason for this discrepancy is the high prevalence of cardiac tamponade in patients with neoplastic, tuberculous or purulent pericarditis (which are easily identified by the investigations performed in this protocol), compared with its lower prevalence in patients with pericarditis of other causes (68% vs 28% in patients with effusion). This difference was statistically significant ($p < 0.001$). The different prevalence rates of tamponade in both etiologic categories has been pointed out in retrospective series.[6,14,26] However, no definite guidelines for the indications of pericardiocentesis and biopsy have been established on the basis of this difference.

Diagnostic accuracy is a common issue in any etiologic study. How many objective diagnoses may have been missed by our protocol? The rather low diagnostic yield of stage I (6%) suggests that a number of pericarditides of viral or toxoplasmic origin may not have been identified. Despite the intrinsic difficulties in the diagnosis of viral pericarditis,[27,28] a more systematic use of the studies in stage I may increase the rate of these diagnoses in primary acute pericardial disease. On the contrary, we contend that the strict performance of the protocol allowed the identification of almost all cases of severe and treatable diseases such as tuberculous, purulent or neoplastic pericarditis. Indirect evidence of this assumption is provided by the fact that no patient in whom the invasive procedures failed to identify the cause, had signs of active pericardial or systemic disease at the end of follow-up; moreover, clinical cure had been spontaneously achieved in all but 1 patient in whom subacute effusive-constrictive pericarditis had developed, and in whom pericardiocentesis, biopsy and pericardiectomy had not yielded the diagnosis. Although the possibility of self-limited tuberculous pericarditis has been recognized,[9] it appears to have been an exceptional occurrence in a disease in which classic reports[9,29] point to an unfavorable evolution in almost all cases; therefore, the finding of a good evolution in our cases with negative etiologic investigations appears relevant for clinical practice. The strikingly different pattern of evolution to constrictive pericarditis in patients with tuberculous, neoplastic and purulent disease on the one hand, and in those with idiopathic disease on the other hand (although already known[30]), is also suggestive of a correct etiologic categorization of the latter group.

Choice between pericardiocentesis and pericardial biopsy: Although our global diagnostic yield of pericardiocentesis (19%) and biopsy (22%) was similar, there are qualitative differences between both procedures: (1) Whereas biopsy is more cumbersome and may entail the need for general anesthesia, the risk of undesirable accidents is lower than with pericardiocentesis; therefore, the risk/benefit ratio should be lower than with the latter procedure.[31] (2) Direct histologic examination of the pericardium may allow almost immediate diagnosis in cases of tuberculosis, avoiding the delay inherent in culturing tubercle bacilli. (3) The procedure may allow a direct visualization of the pericardium and, in addition, a quicker and more complete removal of fluid. The choice between "therapeutic" pericardiocentesis and "therapeutic" biopsy may rest on several circumstances such as skill of the cardiologist, availability of a cardiac surgeon, operating-room facilities, severity of hemodynamic impairment, and so on. However, there may be advantages in both approaches. For instance, in the present series, if an emergency surgical drainage had been performed in the 44 patients

undergoing a "therapeutic" pericardiocentesis, 19 subsequent surgical procedures might not have been performed. It can be argued that with needle pericardiocentesis as the selected procedure, in 26 patients this was all that was needed for their correct management without any surgical procedure in the entire course of the disease. The choice, therefore, is circumstantial and must be individualized. A discussion of the choice between both techniques in "diagnostic" indications seems pointless, as our results show little justification for "diagnostic" procedures (diagnostic yield 6%). However, in individual patients in whom severe clinical findings are present, despite the absence of tamponade, a "diagnostic" procedure may be justified. When purulent pericarditis is suspected, the usual clinical setting may make pericardiocentesis desirable. Also, in communities in which tuberculosis is highly prevalent, a "diagnostic" procedure could be advised in patients with persistent illness for more than 3 weeks; in these patients pericardial biopsy should be chosen (despite its global low diagnostic yield) because it is a safe, rapid procedure providing information from both pericardial tissue and fluid.

Spectrum of diagnosis in the present series: Several comments may be appropriate to the spectrum of etiologic diagnoses identified in our study.

Tuberculous pericarditis accounts for 4% of all diagnoses. This is a low prevalence rate in a community in which tuberculosis is still considered to be a significant cause of morbidity; such prevalence is still not high (7%) when only patients who need any invasive procedure are considered (6 of 79). However, considering that tuberculosis is a curable disease, these figures suggest a high enough prevalence to warrant investigation for tuberculosis in cases of pericarditis that are not rapidly self-limited.

Although they reflect a very low prevalence as the presenting feature of neoplasia, the 12 cases in which pericardial involvement was the first manifestation of extracardiac malignancy (5% of our series) constitute a remarkable finding, because it is the most common specific diagnosis in the present study. Although the clinical onset of neoplastic disease with cardiac tamponade is well known,[23,32,33] its prevalence in the whole spectrum of acute pericardial disease is not well documented. Our figures indicate the need of considering the possibility of extracardiac malignancy in cases of acute pericardial disease, most particularly those presenting as tamponade.

The prevalence of toxoplasmic pericarditis is not known.[34] The present series shows that it may not be negligible in some communities. Although it is unlikely that all cases with a high antitoxoplasma IgG titer (9% of all tested cases) correspond to true toxoplasmic pericarditis, the prevalence of the latter is likely to be higher than the 1.8% detected when only the cases with available IgM titer or subsequent IgG titer were analyzed; therefore, the true prevalence rate should lie between 1.8% and 9%. In only 4 patients (1.7% of our series) was a collagen vascular disease identified, in agreement with the notion that isolated pericarditis is rarely the presenting feature of this disease group.[35]

The very low prevalence rate of purulent pericarditis (0.8%) reflects the rarity of this disorder in the absence of risk factors,[36] such as thoracic surgery or immunosuppression, which were not present in the patients included in this study. The true prevalence of viral pericarditis is not known because of the difficulties in its objective diagnosis.[27,28] In fact, isolation of a virus from a pharyngeal swab or from the feces is not sufficient evidence for an unquestionable diagnosis of viral pericarditis. Despite extensive study, by far the most prevalent diagnosis in our series was acute idiopathic pericarditis (86%). We believe that if a significant reduction of this figure is to be realized, a wide range of routine sophisticated virologic and serologic studies should be carried out, with a dubious cost/efficacy ratio for clinical purposes.

Limitations: Considering that with invasive procedures an etiologic diagnosis was achieved in only 20 of 79 patients (25%), the present study could be considered too aggressive, because 36 patients underwent more than 1 invasive procedure, and, moreover, only 1 new diagnosis was made in stage III. These data suggest that it may be advisable to simplify the protocol by unifying stages II and III, and by limiting "diagnostic" procedures. If only "therapeutic" procedures had been applied, the rate of diagnostic results would have been 35%. However, caution must be used when limiting invasive procedures, because we contend that a judicious use of them is justified by 2 considerations: (1) Owing to the strict use of our protocol, in virtually no patient was the diagnosis of tuberculous, neoplastic or purulent pericarditis missed; and (2) at no time was blind antituberculous therapy required, because etiologic information from stages I to III was sufficient to rule out tuberculosis (the single most prevalent curable disease), no patient having reached stage IV.

Clinical implications: (1) "Diagnostic" pericardiocentesis as a routine method is not warranted in the management of acute pericardial disease, except if there is a clinical suspicion of purulent pericarditis. (2) A "diagnostic" procedure is only indicated in individual patients, such as in patients with illness longer than 3 weeks, and belonging to a community with high prevalence of tuberculosis; in these few instances, pericardial biopsy should be chosen because it is safe and provides information from both pericardial tissue and fluid. (3) The choice between "therapeutic" pericardiocentesis and "therapeutic" biopsy must be considered on an individual basis. (4) Although some parts of the present protocol may be controversial, we believe that only through a systematic approach can a substantial diagnostic yield be reached in patients with primary acute pericardial disease.

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Post–Cardiac Injury Syndrome and an Increased Humoral Immune Response Against the Major Contractile Proteins (Actin and Myosin)

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To better understand the pathogenesis of the post–cardiac injury syndrome (PCIS) 2 models of cardiac injury were studied. One hundred twenty-nine patients who underwent cardiac surgery and 80 patients with acute myocardial infarction (AMI) were prospectively followed and the levels of anti-heart antibodies (AHA), anti-actin antibodies (AAA) and anti-myosin antibodies (AMA) were determined. In the surgical group, PCIS developed in 27 patients (21%) and incomplete PCIS in 36 (28%). In the AMI group, PCIS did not develop in any patient, but incomplete PCIS developed in 11 patients (14%) ($p < 0.001$). The surgical group showed a significantly higher humoral immune response than the AMI group when analyzed for AHA and anti-contractile protein antibodies. After cardiac surgery, AHA developed in 59 patients (46%), AAA developed in 33 (26%) and AMA developed in 49 (38%); in the AMI group, significant levels of AHA, AAA and AMA developed in 16 (20%), 7 (9%) and 13 patients (16%), respectively. These studies show a significant correlation between the PCIS clinical classification and auto-antibodies raised against heart contractile proteins.

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The postpericardiotomy syndrome is a frequent complication after cardiac surgery.[1–6] It is characterized by the persistence or occurrence of fever, leucocytosis and signs of pericardial and often pleural reaction, frequently with effusion and pneumonitis after the first postoperative week. Dressler et al[7,8] described a similar illness, the post–acute myocardial infarction (AMI) syndrome. The prevalence varies from 0 to 6% of cases with AMI in different studies.[8–14] Since other forms of cardiac injury give rise to a similar complication, this syndrome is now generally referred to as post–cardiac injury syndrome (PCIS).[15] Although these syndromes are strikingly similar and have been well defined clinically, their pathogenesis remains unclear. The clinical observation that these syndromes appear 7 or more days after the acute injury and are sensitive to corticosteroid therapy suggests that immunologic factors are involved in the pathogenesis. The finding of anti-heart antibodies (AHA)[2–5] and circulating immune complexes[16,17] in sera of most of these patients supports this view.

AHA have been determined by an indirect immunofluorescence technique and different patterns have been described.[5,18] We have shown that antibodies producing a cross-striated pattern in heart tissue are mainly directed against the major contractile proteins, actin and myosin.[19]

The present study compares clinical events following 2 important models of cardiac injury (cardiac surgery and AMI) and determines serially humoral immune response against myocardial muscle cells and especially against the major contractile proteins, actin and myosin.

Methods

The cardiac surgery group consisted of 129 adult patients (26 women, 103 men), aged 43 to 70 years (mean 57). Nineteen patients had undergone aortic valve replacement, 14 mitral valve replacement, 10 combined valve replacement and 86 aorto coronary bypass procedures. The AMI group consisted of 80 patients (15 women, 65 men), aged 42 to 86 years (mean 64).

Patients were grouped according to the degree of PCIS: (1) those who fulfilled the 3 classic features of the PCIS after the first post-injury week—fever, pericarditis and laboratory evidence for inflammation (complete PCIS); (2) those who fulfilled 2 of the main features (incomplete PCIS); and (3) those who showed only 1 or none of the main features (no PCIS).

Serum samples were collected before surgery and 1 to 60 days after operation or after AMI. Sera from 40 patients without obvious cardiovascular disturbances, matched for sex and age, were used as controls. All sera were stored at −20°C and analyzed within 10 months.

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TABLE I Occurrence of Post-Cardiac Injury Syndrome (PCIS) in the Two Study Populations: Clinical Classification

	Cardiotomy (n = 129)	Infarction (n = 80)	p*
PCIS	27 (21%)	0 (0%)	
Incomplete PCIS	36 (28%)	11 (14%)	<0.001
No PCIS	66 (51%)	69 (86%)	

* Chi-square analysis comparing the incidence of PCIS, incomplete PCIS and no PCIS after cardiotomy and infarction.

TABLE II Occurrence of Anti-Heart Antibodies (AHA), Anti-Actin Antibodies (AAA) and Anti-Myosin Antibodies (AMA) After Cardiotomy and Acute Myocardial Infarction

	Cardiotomy	Infarction	p*
AHA	59 (46%)	16 (20%)	<0.001
AAA	33 (26%)	7 (9%)	<0.005
AMA	49 (38%)	13 (16%)	<0.002

* Chi-square analysis comparing the incidence of AHA, AAA and AMA after cardiotomy and infarction.

Anti-heart antibodies: The indirect immunofluorescence technique of Coons and Kaplan[20] was used. Monkey heart muscle, frozen in liquid nitrogen, was cut into sections 4 μm thick in a cryostat at −20°C, mounted on slides and incubated for 20 minutes with 1/10 diluted test serum to be investigated. Four patterns of immunofluorescence staining were distinguished: cross-striated, diffuse intracellular, intercalated disc and heart muscle membrane fluorescence. In this study we concentrated on the cross-striated fluorescence pattern. The intensity of fluorescence staining was graded 0 to +4; only fluorescence of grade +2 or higher was considered positive in this study.

Anti-actin and anti-myosin antibodies: The indirect enzyme-linked immunosorbent assay was used for the quantitation of anti-actin autoantibodies (AAA) and anti-myosin autoantibodies (AMA).[21] The conjugate used for the assay was alkaline phosphatase conjugated goat anti-human IgG (Sigma Chemicals). Rabbit muscle heavy meromyosin (HMM, Sigma) and bovine cardiac actin, prepared according to the method of Spudich and Watt[22] were coated overnight at 4°C onto glutaraldehyde coated immunobeads (Plastic Ball Co.). Sera were added in dilutions of 1/10 to 1/100000 and incubated at 37°C for 2 hours. After washing, the amount of enzyme bound was assayed using N-nitrophenyl phosphate disodium (Sigma Chemicals) as substrate. The reaction was terminated by the addition of 1 N Na OH. The absorbance of test beads was measured on a Vitatron spectrophotometer at a wavelength of 410 nm. Samples that exceeded the mean value of the control group by 2 standard deviations were considered as positives in this study.

Statistics: The significance of differences between incidences was evaluated by the chi-square test.

Results

Post-cardiac injury syndrome: Following our clinical classification, we found that in the surgical group PCIS developed in 27 patients (21%) and incomplete PCIS in 36 (28%) (Table I). The AMI group had a lower complication rate of PCIS; no patient in this group showed complete PCIS and only 11 patients (14%) showed incomplete PCIS.

Correlation between the PCIS clinical classification and the level of anti-contractile protein autoantibodies: The results summarized in Table II indicate that AHA, AMA and AAA are found significantly more often after cardiotomy than after AMI. Quantitative analysis (Table III) showed a direct correlation between the intensity of PCIS and the titer of

TABLE III Occurrence and Intensity of Anti-Heart Antibodies, Anti-Actin Antibodies and Anti-Myosin Antibodies in the Three Groups After Cardiotomy and Acute Myocardial Infarction

	Cardiotomy				Infarction				
Anti-Heart Antibodies									
Intensity	n	2+	3+	4+	n	2+	3+	4+	p†
PCIS	27	27	27	7	0	. . .	. . .	. . .	ND
Inc PCIS	36	20	15	0	11	6	4	0	NS
No PCIS	66	12	7	0	69	10	6	0	NS
p*		p <0.001	p <0.001	p <0.001		p <0.01	p <0.05	ND	
Anti-Actin Antibodies									
Intensity	n	2 SD	4 SD	6 SD	n	2 SD	4 SD	6 SD	p †
PCIS	27	18	15	4	0	. . .	. . .	. . .	ND
Inc PCIS	36	9	6	1	11	4	2	o	NS
No PCIS	66	6	1	0	69	3	0	0	NS
p*		p <0.001	p <0.001	p <0.005		p <0.005	p <0.02	ND	
Anti-Myosin Antibodies									
Intensity	n	2 SD	4 SD	6 SD	n	2 SD	4 SD	6 SD	p†
PCIS	27	25	20	11	0	. . .	. . .	. . .	ND
Inc PCIS	36	16	11	0	11	7	3	0	NS
No PICS	66	8	3	0	69	6	2	0	NS
p*		p <0.001	p <0.001	p <0.001		p <0.001	p <0.02	ND	

Anti-heart antibody fluorescence intensity is graded from 2+ to 4+; the standard deviation index is used for quantitation of anti-actin and anti-myosin antibodies. The number of "positive" patients showing the indicated fluorescence intensity or standard deviation index are shown in each clinical group.

* Chi-square analysis comparing the frequency of anti-heart, anti-actin and anti-myosin antibodies with the clinical classification.

† Chi-square analysis comparing concurrent groups after cardiotomy and infarction.

Inc = incomplete; ND = not done; NS = not significant; SD = standard deviation.

antibodies as determined either by the indirect immunofluorescence technique using frozen sections of heart tissue or by the ELISA technique using actin and/or myosin as antigens.

This is illustrated by the fact that in each group analyzed, the highest intensity of PCIS correlates well with the highest frequency of high titer antisera (e.g., 7 high level AHA [>4] were only found in the group with complete PCIS). Similar results were obtained when searching for AAA or AMA. Generally higher antibody titers were observed when myosin was used as antigen than actin.

Discussion

In this report we have studied 2 models of cardiac injury (cardiac surgery and AMI) both at the level of the PCIS and at the level of auto-antibodies directed against heart tissue and its major contractile proteins, actin and myosin. In agreement with previous studies[3–5,8–14] PCIS was found significantly more frequently and at significantly higher levels in patients who had undergone cardiac surgery than in patients with AMI. In correlation with these clinical results, the immune response was significantly more important after cardiac surgery than after AMI, and a clear correlation was observed between PCIS clinical classification and the levels of specific auto-antibodies against actin and myosin.

Myocardial injury during operation or during AMI is accompanied by the release of cellular proteins or protein-complexes that may function as auto-antigens leading to the formation of what has been referred to as AHA. Actin and myosin are the major constituents of the heart cellular proteins, and thus are likely to be good candidates to trigger the immune response. It has been shown[19] that auto-antibodies generated after cardiotomy, giving a cross-striated fluorescence pattern, are mainly directed against the major contractile proteins, actin and myosin. Cardiac surgery led more frequently to both higher levels of auto-antibodies against actin and myosin and more frequently to PCIS than AMI, although the latter normally gives rise to a more important myocardial damage. Apparently, cardiac surgery is more immunostimulating than infarction. This may be because: (1) Viral infection may, occur during surgery and trigger the immune response.[23,24] (2) The exposure to air or to chemicals (disinfectants) of cardiac tissue may denature a fraction of the released proteins so that they become more immunogenic than the native molecules. (3) The action of anesthetic agents may change immune response. (4) Antigens are massively released in a short period of time during cardiac surgery, whereas after AMI antigens may be released more slowly and during a longer period.

Consistently higher levels of auto-antibodies against myosin than against actin were found. This may be explained by the higher antigenicity of myosin but also by the fact that actin is known to form stable complexes with at least 2 known serum constituents—the vitamin D binding protein[25] and serum gelsolin[26]—so that it may become less immunogenic.

Our studies reveal a good correlation between the release of typical major heart muscle antigens, the corresponding immune response and the concomitant inflammatory reaction. However, further investigations are necessary to detect additional interfering factors and to see if this phenomenon may be generalized to other diseases associated with important cell death.

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Cardiovascular Deconditioning Produced by 20 Hours of Bedrest with Head-Down Tilt (−5°) in Middle-Aged Healthy Men

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Cardiovascular deconditioning after prolonged bedrest has been attributed to inactivity. To examine the role of the altered distribution of body fluids, 5 healthy men, aged 41 to 48 years, were studied before, during and after a 20-hour period of bedrest with head-down tilt (−5°). This intervention produces a marked central shift of intravascular and interstitial fluid, but the short duration minimizes the effects of inactivity. Central venous pressure, cardiac output and stroke volume all increased significantly ($p < 0.05$) from supine baseline mean values; central venous pressure from 8.6 to 12.6 cm H_2O, cardiac output from 6.9 to 7.9 liters/min, and stroke volume from 104 to 113 ml after 15 minutes of tilt, but all values returned to baseline within 20 hours. Supine central venous pressure after tilt was 7.4 cm H_2O, cardiac output 5.7 liters/min and stroke volume 84 ml. Blood volume decreased 0.51 liters. After tilt, orthostatic stress produced a higher heart rate (90 ± 18 vs 68 ± 12 beats/min). Maximal oxygen consumption decreased (2.36 ± 0.41 vs 2.62 ± 0.48 liters/min), mainly owing to reduced stroke volume (87 ± 22 vs 107 ± 18 ml, $p < 0.05$). Thus, tilt produced a transient increase in central venous pressure, stroke volume and cardiac output, but supine mean values were below baseline levels after 20 hours. The post-tilt state was qualitatively and quantitatively similar to that seen after 2 to 3 weeks of bedrest or several days of spaceflight. These results are also similar to those from a previously studied group of ten 20- to 30-year-old normal men. However, the increase in central venous pressure tended to be larger and of longer duration in the middle-aged group. Furthermore, in the young men the initial increase in stroke volume produced relative bradycardia, with no change in cardiac output and arterial pressure. Cardiac output increased in the middle-aged group, but arterial pressure was controlled by vasodilatation. Heart rate did not change. The results support the concept that cardiovascular deconditioning after bedrest is primarily an adaptation to a postural fluid shift rather than to inactivity. Age-related differences in hemodynamic responses to central fluid shifts appear to be present.

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Prolonged bedrest causes cardiovascular deconditioning with orthostatic intolerance and decreased exercise capacity.[1–4] The mechanisms of these responses are unknown, but prolonged inactivity is generally believed to be a major factor. However, previous studies[5,6] in our laboratory in young healthy subjects have shown that a 24-hour period of bedrest with a 5° head-down tilt, introduced by Kakurin et al[7] as a means of simulating 0 gravity, produces the intravascular volume loss and cardiovascular deconditioning seen with 2 to 3 weeks of bedrest. These results suggest that an adaptation to a central fluid shift associated with the supine position, rather than inactivity per se, may be a major factor producing deconditioning after bedrest. The present study was performed to determine the extent and mechanisms of bedrest deconditioning in men comparable in age to symptomatic patients with acquired heart disease and to compare the responses to these middle-aged men with those of younger subjects studied previously.[5,6]

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Methods

Subjects: Five sedentary men, 45 ± 3 years old (range 41 to 48), were recruited from the liberal arts faculty of a local university (Table I). None had participated in medical research previously, but volunteered on the basis of a notice posted on campus. These subjects were the first 5 who contacted our office.

Procedures: Procedures were reported in detail previously.[5,8] Briefly, indirect blood pressure was measured with a semiautomated cuff device (Narco Bio-systems Electro-

sphygmomanometer PE 300), heart rate by electrocardiogram (Frank X,Y,Z leads), forearm flow and venous compliance by venous occlusion plethysmography, leg volume during bedrest by measurements of leg circumferences and Simpson's rule, cardiac output by an acetylene rebreathing technique (coefficient of variation 4.3% over the range of 5 to 19 liters/min), blood volume by simultaneous measure of red cell mass (Cr^{51}) and plasma volume (radioiodinated serum albumin I^{131}) and plasma renin activity by radioimmunoassay. Exercise was performed upright on a mechanically braked bicycle ergometer (Monark) with progressive increases in workload every 4 minutes until maximal effort was achieved. Maximal oxygen consumption was defined as the level at which heart rate and oxygen consumption failed to increase despite an increased workload, and was measured by collection of expired air in a Douglas bag and analyzed by mass spectrometer and Tissot spirometer. Lower body negative pressure with 3 to 5 minutes at levels of −16, −32, −40 and −50 mm Hg was obtained with a device developed for use during the Skylab flights. The subjects were supine (0° tilt). Leg volume changes during lower body negative pressure were estimated by a double-stranded, mercury-in-silastic strain gauge placed around the calf at the level of its maximal girth. Central venous pressure was measured with a catheter inserted percutaneously and positioned fluoroscopically. The anterior and lateral chest walls were marked to provide 3-dimensional reference coordinates for positioning the pressure transducer.

Protocol: After the subjects gave informed written consent, a physical examination, complete blood count, SMA-12 and urinalysis were performed. Subject familiarization included tours of the laboratory and clinical research center and short periods of exercise (300 kpm for 6 minutes) and lower body negative pressure (−32 mm Hg). After at least 1 hour of rest, lower body negative pressure was repeated (−50 mm Hg) and a maximal bicycle stress test performed.

On the morning of the tilt procedure, the subject reported to the laboratory in a fasting state, where blood samples were drawn, a central venous pressure catheter was inserted and blood volume was measured. The subject was then ambulatory and ate a light breakfast. One to 3 hours later, lower body negative pressure (−50 mm Hg) was repeated. The subjects were again ambulatory for 1 to 2 hours until approximately 1 hour after lunch, when baseline measures were repeated. The 5° head-down tilt was begun within 30 minutes and continued for 20 hours. The subjects received a 4-g sodium diet and fluids ad lib. After the tilt period, baseline measurements were repeated with the subject supine (0°), during lower body negative pressure and sitting on the bicycle. The central venous pressure catheter was removed immediately before exercise.

Statistical analysis included paired t tests or repeated measures analysis of variance with Student-Newman-Keuls test for individual differences.[9] Occasional data points (<0.5%) for individual subjects were interpolated when measurement at a specific time was not available. All values are reported as the mean ± standard deviation. A significance level of $p \leq 0.05$ was used.

Results

All 5 subjects completed the bedrest study without complications, except 1 subject with marked vagotonia before the study. He had a brief period of asystole followed by bradycardia during the post-tilt lower body negative pressure stress and required intravenous atropine to restore normal sinus rhythm. None of the subjects complained of the nasal congestion or stuffiness frequently reported in head-down tilt or spaceflight, but minor musculoskeletal complaints were universal.

TABLE I Characteristics of the Five Study Subjects

Age (yr)	45 ± 3
Height (cm)	179 ± 6
Weight (kg)	88 ± 12.9
$\dot{V}O_2$ max (ml·kg^{-1}·min^{-1})	30 ± 6.1
Total blood volume (liters)	6.28 ± 0.30

Values are mean ± standard deviation.
$\dot{V}O_2$ max = maximal oxygen consumption.

The initial hemodynamic responses to the 5° head-down tilt were evident within 15 minutes (Fig. 1). Central venous pressure increased from 8.6 ± 2.7 cm H_2O to 12.6 ± 2.5 cm H_2O after 15 minutes of head-down tilt and was associated with an increase in stroke volume (from 104 ± 8 to 113 ±16 ml) and cardiac output (from 6.9 ± 1.4 vs 7.9 ± 1.4 liters/min) ($p \leq 0.05$). Heart rate, blood pressure and forearm blood flow had not changed significantly at this time. After 4 hours, central

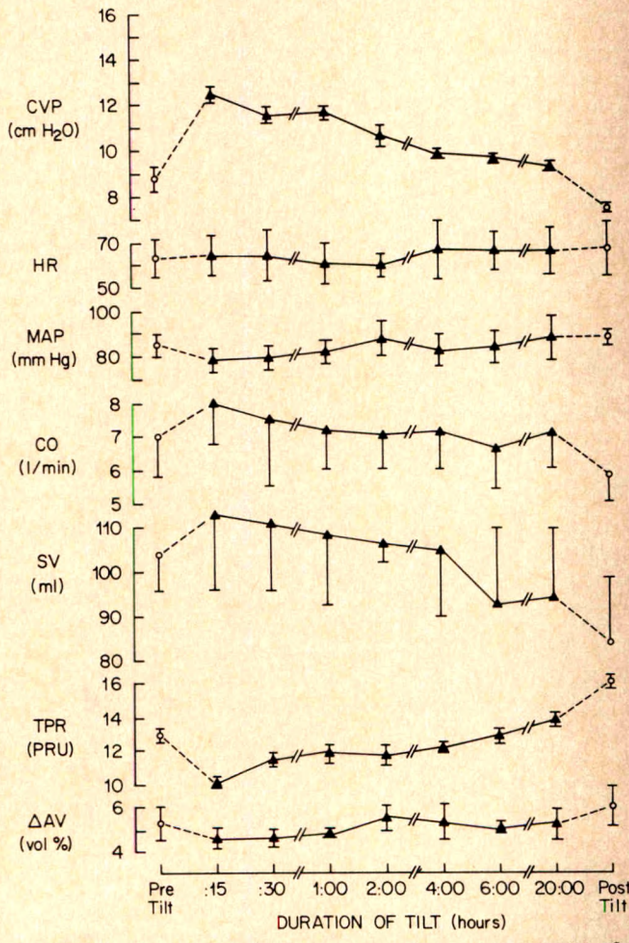

FIGURE 1. The hemodynamic responses to head-down tilt (−5°). Measurements before and after bedrest in the supine position were taken within 10 minutes of tilt. Stroke volume (SV) and central venous pressure (CVP) were significantly elevated by tilt and were significantly lower after tilt ($p < 0.05$). Values are mean ± standard deviation. ΔAV = calculated arteriovenous difference for oxygen; CO= cardiac output; HR = heart rate; MAP = mean arterial pressure; TPR = total peripheral resistance.

venous pressure was still elevated, but cardiac output and stroke volume returned almost to baseline values before tilt. Although central venous pressure was slightly elevated for the duration of the tilt, other measurements returned to pre-tilt levels by 4 to 6 hours. Leg volume decreased from 17.24 ± 2.51 to 16.96 ± 2.30 liters after 20 hours of bedrest.

During head-down tilt, peripheral venous hematocrit increased from 41.8 ± 1.5% to 44.2 ± 2.2% ($p < 0.04$). Urine output was 2.19 ± 0.30 ml/min during the first 6 hours of tilt, but only 1.55 ± 0.11 ml/min in the subsequent 10 hours. Hourly sodium excretion followed a similar pattern, 16.4 ± 3.3 vs 5.3 ± 1.5 mEq/hour in hours 0 to 6 and 7 to 16, respectively. Plasma renin activity decreased in the first 6 hours of tilt from (0.17 ± 0.02 vs 0.65 ± 0.20 $ng \cdot ml^{-1} \cdot min^{-1}$), but returned to baseline by 16 hours (0.42 ± 0.20 $ng \cdot ml^{-1} \cdot min^{-1}$). When the subjects resumed the supine position after tilt, central venous pressure (−14%), stroke volume (−19%) and cardiac output (−17%) were lower in all subjects ($p \leq 0.05$). The differences in stroke volume (−26%) and heart rate (+31%) were even greater when the subjects were sitting before exercise.

The tolerance to lower body negative pressure was decreased by the 20 hours of head-down tilt (Fig. 2). All subjects tolerated a −50-mm Hg level before tilt, but 4 were presyncopal at the −40-mm Hg level after tilt. Signs included lightheadedness, heart rate instability and paradoxical vasodilation. Central venous pressure decreased during lower body negative pressure before and after tilt to a similar degree and cardiac output was likewise maintained at an almost identical level compared with values before tilt; however, heart rate was substantially higher and stroke volume lower. Total peripheral resistance and mean arterial blood pressure did not differ at rest or at −16 mm Hg, but at maximal lower body negative pressure, tended to be slightly higher after tilt. Forearm blood flow was higher at rest and at −40 mm Hg lower body negative pressure after tilt (6.6 ± 2.2 to 5.9 ± 2.3 vs 4.4 ± 0.8 to 3.5 ± 0.8, ml/100 ml/min, rest and −40 lower body negative pressure, $p < 0.05$), while leg volume changes were not significantly different at −40 mm Hg lower body negative pressure.

A significant deconditioning effect was seen in all 5 subjects (Fig. 3). Although stroke volume fell by 19%, a slightly higher heart rate (169 ± 12 vs 164 ± 13 beats/min) and a wider atrioventricular oxygen difference (16.4 ± 2.7 vs 13.3 ± 2.3, vol%) resulted in a de-

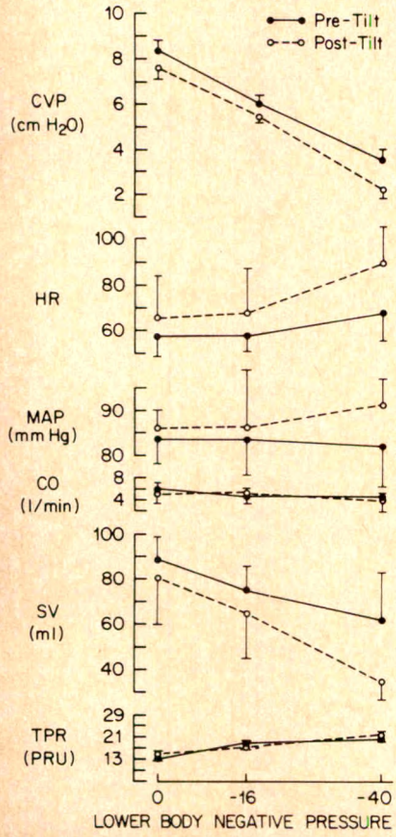

FIGURE 2. Response to lower body negative pressure before (**solid line**) and after (**dashed line**) a 20-hour period of bedrest with −5° head-down tilt. Abbreviations are as in Figure 1.

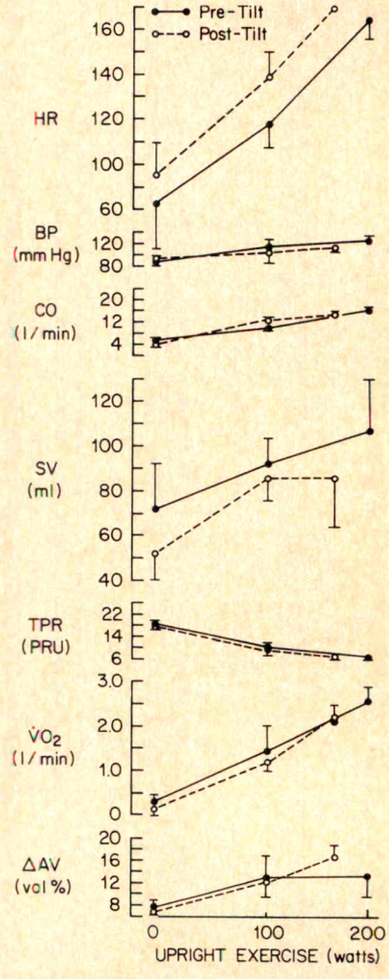

FIGURE 3. Responses to upright exercise before and after bedrest with −5° head-down tilt. Heart rate (HR) is significantly higher and stroke volume (SV) lower at maximal exercise after tilt ($p < 0.05$). BP = blood pressure; $\dot{V}O_2$ = oxygen consumption; other abbreviations as in Figure 1.

crease in maximal oxygen consumption of only 10%. Maximal cardiac output and mean arterial pressure both decreased while total peripheral resistance was unchanged.

Discussion

During and after head-down tilt, the hemodynamic and endocrine responses of this group of middle-aged men were qualitatively similar to those of younger subjects undergoing comparable periods of bedrest with head-down tilt.[5,6] However, increases in central venous pressure were somewhat greater and increases in stroke volume persisted somewhat longer in the middle-aged subjects. The older subjects increased cardiac output transiently during early tilt, but maintained a relatively constant arterial pressure with a substantial drop in total peripheral resistance. In contrast, in our younger subjects moderate bradycardia developed, which kept cardiac output and, therefore, blood pressure, constant. Corresponding age-related differences have been seen during orthostasis in hypovolemic symptomatic patients with mitral valve prolapse.[10] The older patients used vasoconstriction as a primary means of regulating blood pressure, whereas in younger patients tachycardia was more likely to develop. The results emphasize the fact that characterization of baroreflexes must include measures of peripheral resistance as well as heart rate.

The exact amount of fluid shifted into the central compartment with head-down tilt is not known, because both splanchnic and lower limb venous beds are involved and estimates of the former are difficult. The measured volume loss from the legs was approximately 300 ml. This finding is consistent with the data of Echt et al,[11] which would predict a central shift of at least 500 ml to produce comparable central venous pressure increases. Effective systemic venous compliance was not measured in these older subjects, but a prior study suggests that prolonged changes in effective systemic venous compliance are not an important response to bedrest.

Loss of salt and water with a decrease in intravascular and interstitial volume appear to be more important compensatory mechanisms. Sodium and water excretion over the first few hours of bedrest with head-down tilt increased to provide rapid readjustment of central venous pressure to pre-tilt levels. Our previous studies suggest that plasma renin, aldosterone and antidiuretic hormone levels are all reduced acutely and mediate diuresis.[5,6] Plasma renin activity showed a similar decrease in the present study.

Several lines of evidence argue against inactivity being the major cause of deconditioning after bedrest. First, this and previous studies of short periods of bedrest with head-down tilt[5,6] documented deconditioning in the absence of any prolonged inactivity. Myocardial and musculoskeletal adaptations to inactivity would be measured in days to weeks rather than the 20 hours of inactivity used in our studies. Second, exercise in the supine position during bedrest, with programs ranging from heavy dynamic exercise to static efforts,[12] generally fails to prevent the development of cardiovascular dysfunction. Several studies of supine exercise during bedrest, recently reviewed by Blomqvist and Stone,[4] showed little or no protection. Third, if inactivity is a major factor, physical training should accelerate recovery, but this was not found in a recent study by DeBusk et al.[13] These investigators postulated that the mere exposure to orthostatic stress was sufficient to overcome the deconditioning associated with bedrest. These data, combined with the fact that prolonged bedrest, head-down tilt, upright water immersion and spaceflight produce similar states of cardiovascular dysfunction, suggest that the primary cause is a response to an altered distribution of body fluids and intravascular pressures. The common denominator of these interventions is a cephalad fluid shift and a transient increase in cardiac filling pressure.[4]

Several mechanisms contribute to the orthostatic intolerance of bedrest-induced deconditioning. Decreased intravascular volume is a significant factor. In our subjects blood volume decreased 8%, a level comparable to that reported previously.[4,14,15] However, the response to an acute volume loss of this magnitude is less severe than the orthostatic intolerance produced by bedrest. Ekblom et al[16] measured maximal oxygen uptake in healthy young adults before and after phlebotomy of 800 ml of whole blood. Although this reduced hemoglobin concentrations by almost 13%, maximal oxygen consumption decreased by only 6%. Similar results were obtained by Saltin,[17] who examined work capacity in normal subjects before and after heat-induced dehydration. Our subjects had a larger decrease in maximal oxygen consumption despite smaller changes in blood volume. In addition, attempts to rehydrate subjects after bedrest or to prevent the blood volume loss have not corrected the deconditioning. Neither direct infusion of normal saline solution[6] nor administration of mineralocorticoid[18] are effective countermeasures.

Our studies after tilt showed significant hemodynamic changes in both the upright and the supine position. Filling pressure and stroke volume were reduced. Saltin et al[2] and Hung et al[19] showed that the stroke volume reduction persists also during supine exercise. The decreased stroke volume is probably a result of reduced preload because cardiac contractility is unchanged.[5,6,20]

The cardiovascular deconditioning induced by bedrest and tilt is generally more apparent in the upright position. Increased compliance of the leg veins with venous pooling could contribute, but estimated calf volumes during lower body negative pressure before and after bedrest in the present study were not different. Alternatively, bedrest and tilt may cause impairment of the reflex mechanisms that normally maintain arterial blood pressure and tissue perfusion in the upright position. Altered baroreflexes after bedrest in monkeys were reported by Billman et al,[20] but similar data in humans are lacking. Arterial vasoconstrictor responses during lower body negative pressure after head-down tilt in our subjects were unchanged, although one may argue that a greater response should have occurred in the presence of hypovolemia after tilt.

Recent studies have identified additional neural mechanisms that may participate in postural cardiovascular responses. Henriksen and Sejrsen[21] described a local reflex that causes vasoconstriction in skeletal muscle and subcutaneous fat in response to venous distension. Thompson and Yates[22] showed that stimulation of venous afferents that respond to stretch increases skeletal muscle tone by a spinal reflex. The effect of bedrest on these reflexes has not been examined.

Other aspects of neurohumoral cardiovascular control mechanisms have been studied, but no clear concepts have emerged. Indirect support for a change in peripheral vascular regulation, mediated by modulation of central mechanisms, is found in a recent report by Norsk et al.[23] Chobanian et al[3] found no bedrest-induced changes in pressor responses to norepinephrine or angiotensin infusions. Schmid et al[24] also found normal vasoconstrictor responses to intraarterial norepinephrine infusions but attenuated effects of tyramine, suggesting normal receptor function but impaired endogenous release.

Clinical implications: Despite the lack of complete understanding of cardiovascular impairment after bedrest, several observations of possible relevance to the cardiac patient can be made. Most important, the central fluid shift and not inactivity is the major factor. Apparently, the reference level or setpoint for central blood volume regulation in man is the upright position. A successful adaptation to the supine position includes decreased end-diastolic volume and filling pressures and decreased total blood volume. These losses and impaired regulatory mechanisms make the patient unable to cope effectively with a further decrease in central blood volume and filling pressures, when the upright position is resumed. Exercise with bedrest is not directed toward the primary problem and cannot be expected to prevent deconditioning. Volume expansion has limited effectiveness[6,21] and could be contraindicated in cardiac patients. Reestablishment of normal upright hydrostatic gradients is an effective countermeasure in bedrest studies in normals[4,25] and may play a similar beneficial role in patients.

The results of this study are not directly transferable to the clinical situation. Patients with heart failure are resistant to orthostatic challenges.[26] Nevertheless, the findings provide a rationale for reemphasis of a 40-year-old therapeutic approach. In 1944, Harrison[27] and Dock[28] identified the cardiovascular problems associated with prolonged bedrest. Levine and Lown subsequently published a classic study of chair rest for patients with acute myocardial infarction and found it to be a safe and desirable form of treatment.[29]

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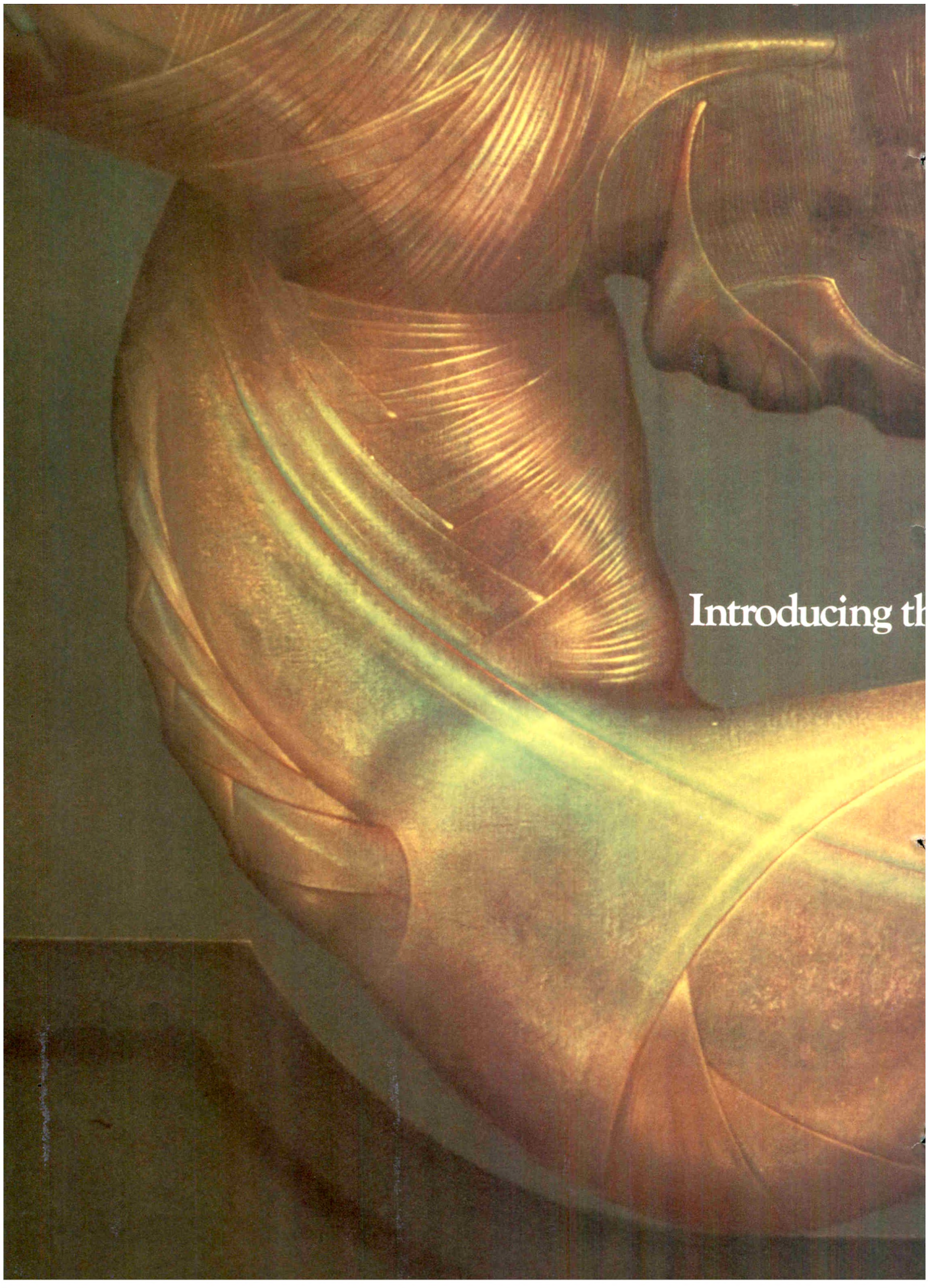
Between man and his medicine lies only a thin barrier...

...the skin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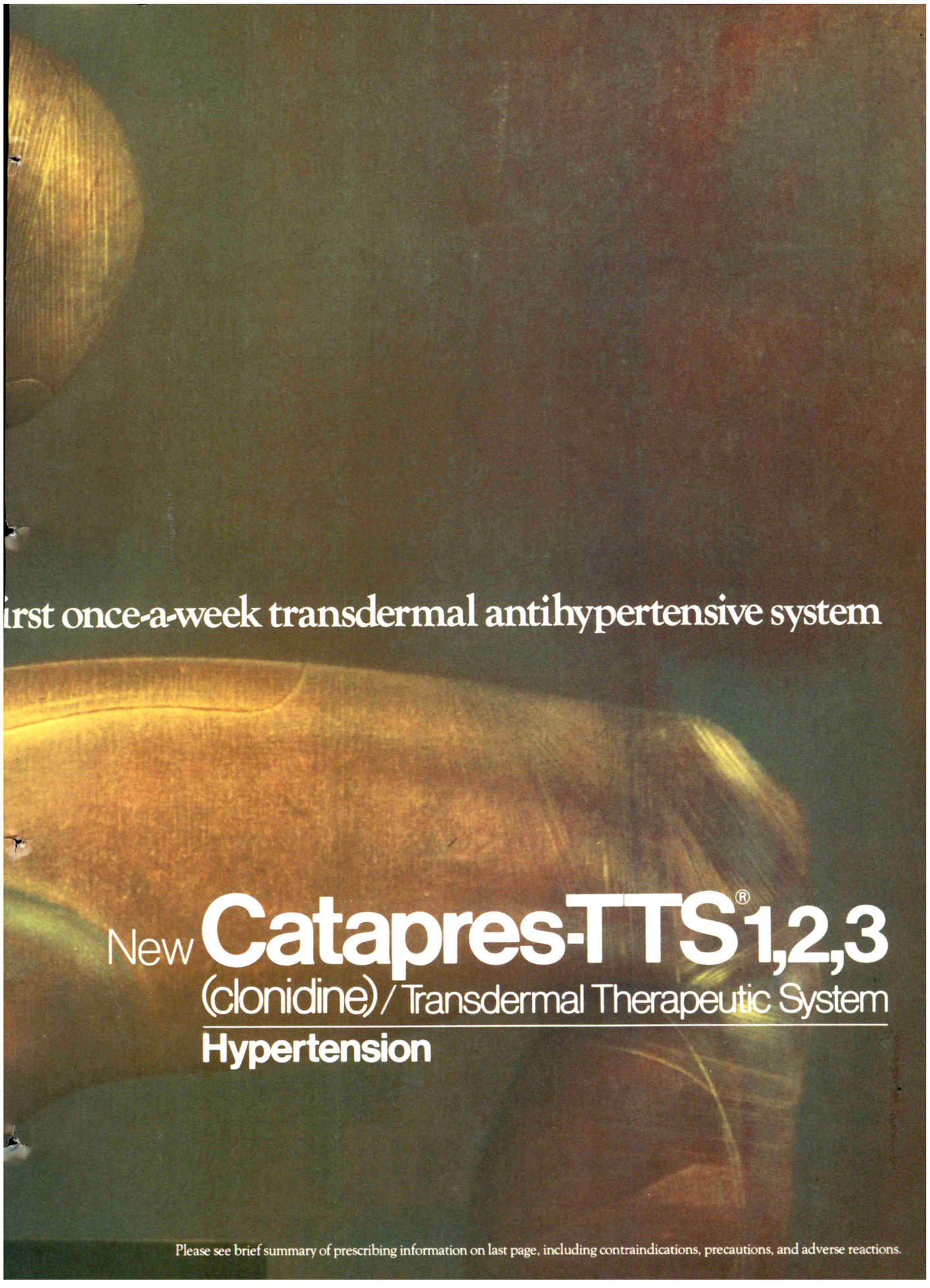
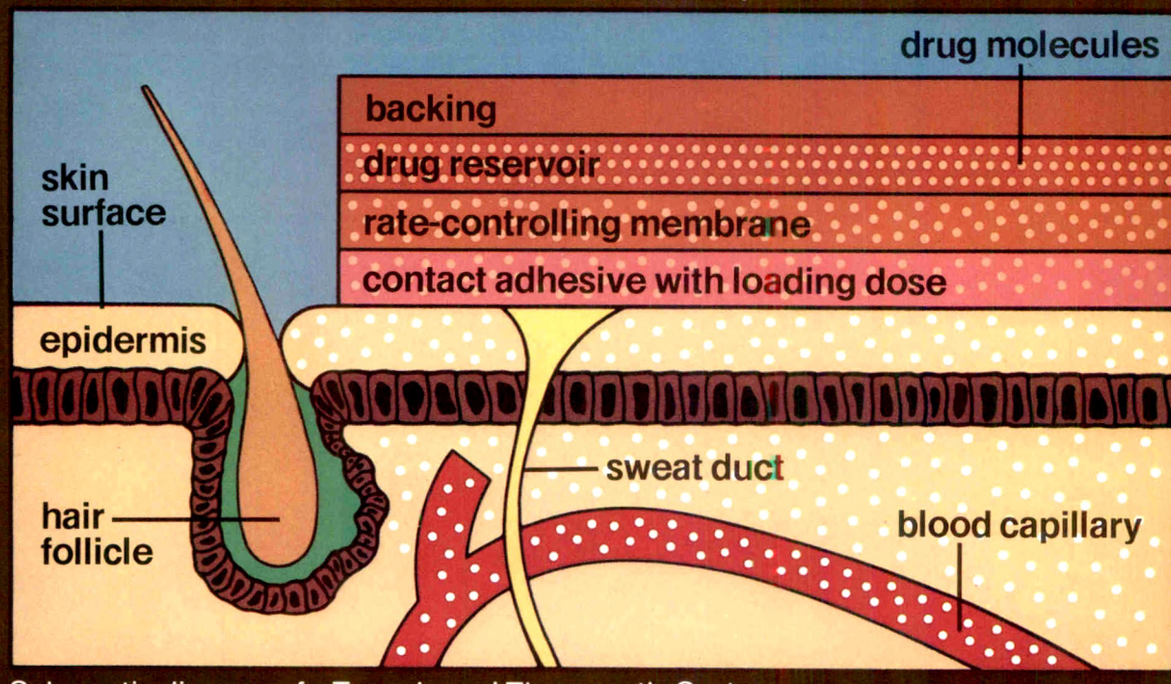

irst once-a-week transdermal antihypertensive system
New Catapres-TTS®1,2,3
(clonidine) / Transdermal Therapeutic System
Hypertension
Please see brief summary of prescribing information on last page, including contraindications, precautions, and adverse reactions.

Continuous 7-day transdermal delivery

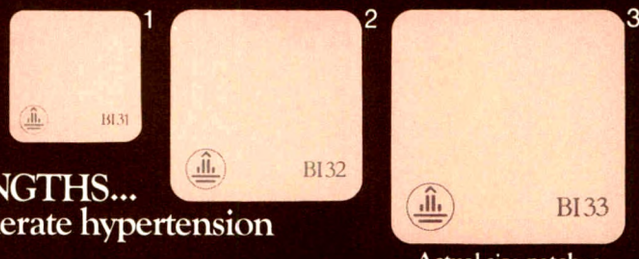


Schematic diagram of a Transdermal Therapeutic System placed in contact with the skin.

New Catapres-TTS®1,2,3

(clonidine) / Transdermal Therapeutic System

Hypertension



Actual size patches

THREE DOSAGE STRENGTHS...
Start with it in mild to moderate hypertension

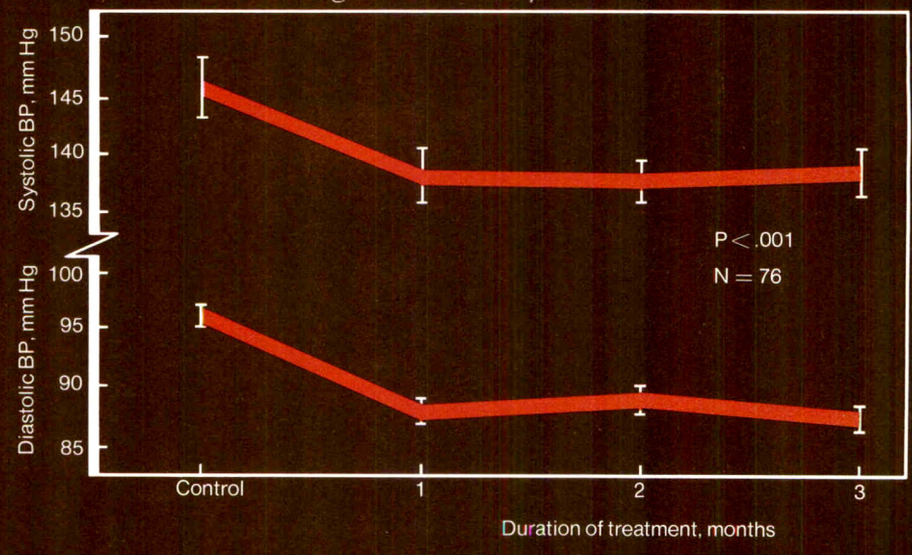
- Convenient once-a-week dosage to aid compliance.
- Effective blood pressure control with or without a diuretic.
- Steady-state blood levels — without the peaks and valleys of oral forms.
- No diuretic-like biochemical effects.
- 24-hour blood pressure control 7 days a week.
- Central control of blood pressure.

Most common side effects are dry mouth and drowsiness, which tend to diminish with time, and mild erythema and pruritus associated with 7-day skin occlusion. After a mean duration of treatment of 24 weeks, contact dermatitis was observed in 16% of patients. This condition resolved upon discontinuation of therapy.

7 days of continuous therapy... a new age of compliance

Documented long-term efficacy

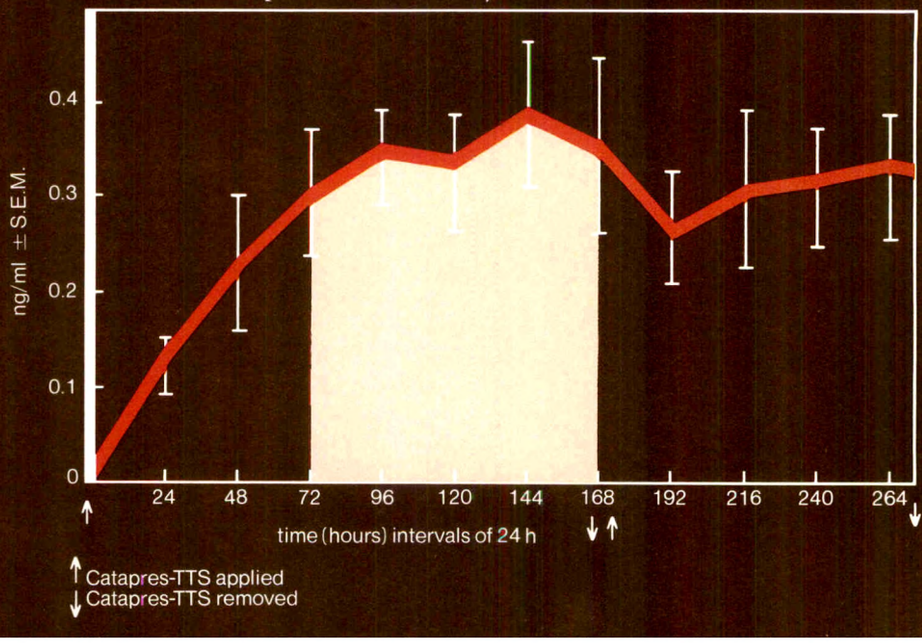
Systolic and diastolic BPs during control (placebo) and after 1, 2, and 3 months of treatment with clonidine administered transdermally. Values are means ± SEMs.[1]



Patch-to-patch applications

Steady-state blood levels — without the peaks and valleys of oral forms

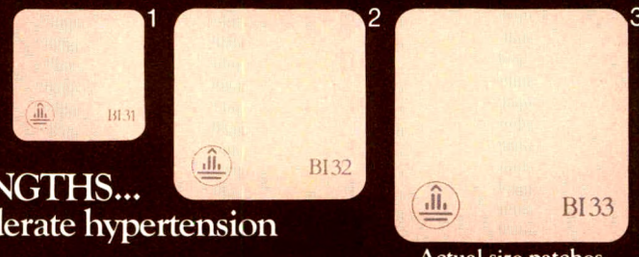
Mean (n = 5) clonidine plasma concentration (ng/ml)—3.5 cm² Catapres-TTS patch.[2]



New Catapres-TTS®1,2,3

(clonidine) / Transdermal Therapeutic System

Hypertension



Actual size patches

THREE DOSAGE STRENGTHS...
Start with it in mild to moderate hypertension

How to use Catapres-TTS®

Three Dosage Strengths for Individualized Therapy
Titrate to proper dosage with Catapres-TTS® alone

1. Start with #1. Replace with #2 and then #3 when necessary to achieve effective blood pressure control.
2. Catapres-TTS® is usually unaffected by showering or other routine daily activities. For some patients, use of an overlay is occasionally required to maintain adequate skin adherence.
3. Most common side effects are dry mouth and drowsiness, which tend to diminish with time, and mild erythema and pruritus associated with 7-day skin occlusion. Contact dermatitis was observed in 16% of patients (100 of 631) treated for a mean duration of 24 weeks. This condition resolved upon discontinuation of therapy.*

Rx

Catapres-TTS 1
x4 Sig: apply once weekly as directed
Refill x2

*Please refer to **Precautions** in prescribing information if considering substitution of oral clonidine hydrochloride in patients who develop skin reactions during Catapres-TTS® therapy.

References:
1. Weber MA et al. Transdermal administration of clonidine for treatment of high BP. *Arch Intern Med* 1984; *144*:1211-13.
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New Catapres-TTS®1,2,3

(clonidine) / Transdermal Therapeutic System

Hypertension

Actual size patches

THREE DOSAGE STRENGTHS...
Start with it in mild to moderate hypertension

The first once-a-week transdermal antihypertensive system

Seven days of effective blood pressure control

- Convenient once-a-week dosage to aid compliance.
- Effective blood pressure control with or without a diuretic.
- Steady-state blood levels—without the peaks and valleys of oral forms

Brief Summary of Prescribing Information

Contraindications: Catapres-TTS® (clonidine) should not be used in patients with known hypersensitivity to clonidine or to any other component of the adhesive layer of the therapeutic system.

Precautions: ***General:*** In patients who have developed localized contact sensitization to Catapres-TTS® (clonidine), substitution of oral clonidine hydrochloride therapy may be associated with development of a generalized skin rash.

In patients who develop an allergic reaction to Catapres-TTS® that extends beyond the local patch site (such as generalized skin rash, urticaria, or angioedema) oral clonidine hydrochloride substitution may elicit a similar reaction.

As with all antihypertensive therapy, Catapres-TTS® should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

Withdrawal: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in subjective symptoms such as nervousness, headache and sweating, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma, but such occurrences have usually been associated with previous administration of high oral doses (exceeding 1.2 mg/day) and/or with continuation of concomitant beta-blocker therapy. Rare instances of hypertensive encephalopathy and death have been reported.

An excessive rise in blood pressure following Catapres-TTS® discontinuance can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving beta-blockers and clonidine concurrently, beta-blockers should be discontinued several days before cessation of Catapres-TTS® administration.

Perioperative Use: As with oral clonidine therapy, Catapres-TTS® therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting Catapres-TTS® therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2 to 3 days after initial application of Catapres-TTS®.

Information for Patients: Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a potential sedative effect of clonidine. Patients should be cautioned against interruption of Catapres-TTS® therapy without a physician's advice. Patients should be advised that if the system begins to loosen from the skin after application, the adhesive overlay should be applied directly over the system to ensure good adhesion over its 7-day lifetime. Instructions for using the system are provided. Patients who develop moderate or severe erythema and/or localized vesicle formation at the site of application, or a generalized skin rash, should consult their physician promptly about the possible need to remove the patch.

Drug Interactions: If a patient receiving clonidine is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage. Clonidine may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives. Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 132-week oral carcinogenicity study in rats, clonidine hydrochloride produced no carcinogenic effects at doses up to 300 times the maximum recommended human dose of Catapres-TTS® on a mg/kg weight basis.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Reproduction studies performed in rabbits at doses up to 3.1 times the maximum recommended daily human dose of Catapres-TTS® have revealed no evidence of impaired fertility or harm to the fetus due to clonidine hydrochloride. Studies in rats and mice revealed that doses of 500 mcg/kg/day and higher are embryotoxic. One rat study at doses of 15 mcg/kg/day (0.33 times the maximum recommended daily human dose) exhibited embryotoxicity. There are no adequate and well-controlled studies in pregnant women. Although animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: As clonidine is excreted in human milk, caution should be exercised when Catapres-TTS® (clonidine) is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been

month, multiclinic trial of Catapres-TTS® in 101 hypertensive patients, the most frequen systemic reactions were dry mouth (25 patients) and drowsiness (12 patients).

Transient localized skin reactions, primarily localized pruritus occurred in 51 patients Twenty-six patients experienced localized erythema. This erythema and pruritus were mor common in patients utilizing an adhesive overlay for the entire 7-day treatment period Allergic contact sensitization to Catapres-TTS® was observed in 5 patients.

In additional clinical experience, contact dermatitis was observed in 100 of 631 patient (about 16 in 100) treated for a mean duration of 24 weeks.

The following less frequent adverse experiences were also reported in patients involved i the multiclinic trial with Catapres-TTS®.

Gastrointestinal: Constipation (1 patient); nausea (1); and change in taste (1).

Central Nervous System: Fatigue (6 patients); headache (5); lethargy (3); sedation (3 insomnia (2); dizziness (2); and nervousness (1).

Genitourinary: Impotence/sexual dysfunction (2 patients).

Dermatological: Localized vesiculation (7 patients); hyperpigmentation (5); edema (3 excoriation (3); burning (3); papules (1); throbbing (1); blanching (1); and generalize macular rash (1).

In additional clinical experience involving 3539 patients, less common dermatologic reac tions have occurred, where a causal relationship to Catapres-TTS® was not established maculopapular skin rash (10 cases); urticaria (2 cases); angioedema involving the face (cases), one of which also involved the tongue.

Oro-otolaryngeal: Dry throat (2 patients).
In long experience with oral clonidine hydrochloride, the most common adverse reaction have been dry mouth (about 40%), drowsiness (about 35%) and sedation (about 8%). I addition, the following adverse reactions have been reported less frequently:

Gastrointestinal: Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, eac about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; parotitis rarely.

Metabolic: Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000; transien elevation of blood glucose or serum creatine phosphokinase, rarely.

Central Nervous System: Nervousness and agitation, about 3 in 100 patients; menta depression, about 1 in 100 and insomnia, about 5 in 1000. Vivid dreams or nightmares, othe behavioral changes, restlessness, anxiety, visual and auditory hallucinations and delirium have been reported.

Cardiovascular: Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycar dia, and bradycardia, each about 5 in 1000. Raynaud's phenomenon, congestive heart fail ure, and electrocardiographic abnormalities (i.e. conduction disturbances and arrhythmias have been reported rarely.

Dermatological: Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneu rotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.

Genitourinary: Decreased sexual activity, impotence and loss of libido, about 3 in 10 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention about 1 in 1000.

Other: Weakness, about 10 in 100 patients; fatigue, about 4 in 100; headache, and discon tinuation syndrome, each about 1 in 100; muscle or joint pain, about 6 in 1000 and cramps o the lower limbs, about 3 in 1000. Dryness, burning of the eyes, dryness of the nasal mucosa pallor, weakly positive Coombs' test, increased sensitivity to alcohol and fever have been reported.

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Safety of Outpatient Cardiac Catheterizations

W. PETER KLINKE, MD, GEORGE KUBAC, MD, TAL TALIBI, MD,
and SIMON J.K. LEE, MD

Since 1979 most of the cardiac catheterizations at the investigators' institution have been performed as outpatient procedures. All cardiac catheterizations performed over a 66-month period were analyzed. A total of 3,071 outpatient cardiac catheterizations (83% of all cardiac catheterizations) were performed. The percutaneous femoral technique was used in 98% of the procedures. Most patients (79%) had both right and left-sided cardiac catheterization and coronary angiography, which showed significant coronary artery disease (70.4%). Only 13.6% of the study results were normal. Thirty-four patients (1.1%) had major complications, including 4 deaths (0.13%). Seventy patients (2.3%) were admitted for observation only. More than 96% of all patients did not have a major complication and were discharged the same day. Thus, outpatient cardiac catheterization can be performed safely, with a potential reduction in hospital costs and better utilization of medical beds.

(Am J Cardiol 1985;56:639–641)

Cardiac catheterization and coronary angiography have become important and integral components in the investigation of patients with cardiovascular disease. Development of cardiovascular surgical techniques and, more recently, balloon angioplasty, has resulted in a dramatic increase in the number of cardiac catheterizations performed. In a busy hospital this can place a burden both on bed utilization and budgets. We herein report our consecutive series of patients undergoing outpatient cardiac catheterizations by the percutaneous femoral method.

Methods

All patients were initially referred to and evaluated by one of us. A complete history, physical examination and necessary investigations were performed before the catheterization. The procedure was explained and consent was obtained at this time.

Criteria for an outpatient study was up to each cardiologist, but in most cases the only reason for not doing an outpatient cardiac catheterization was that the patient was already in the hospital because of complications of cardiovascular disease such as unstable angina, myocardial infarction or congestive heart failure. Most patients came from the metropolitan area. However, several patients from out of town, if stable and accompanied by a relative, were given the option of outpatient cardiac catheterization and stayed overnight with relatives or in a nearby hotel.

Patients were admitted on the day of the procedure to an outpatient day care facility located within the hospital. After the usual preparation the patient was taken to the cardiac catheterization laboratory. Patients were routinely premedicated with 10 mg of Valium® (diazepam) orally, but there was no routine order for nitroglycerin, heparin or atropine.

Hemostasis after the procedure was achieved by manual pressure and the patient was transferred back to the outpatient area for observation. A sandbag was used to assure hemostasis for 4 hours. After this time, if there were no signs of bleeding, thrombosis or hypotension, the patient was allowed to ambulate for 2 hours further and then discharged. A full-time nurse was in attendance to record vital signs and observe for bleeding or loss of pulse during the patient's stay. Upon discharge the patient was advised not to undertake any activities for the remainder of the day. Full activities were allowed the next day. Written instructions were given to each patient to return immediately to the hospital if signs of bleeding or thrombosis occurred. Patients were followed up by their own physicians and cardiologists within a week of discharge.

Results

We reviewed all the consecutive cases done from January 1979 until June 1984. This was done by reviewing both the Catheterization Laboratory log book and a computerized summary record that detailed the procedures and complications on all patients. A medical record search was done to determine which patients had been admitted to the hospital up to a month after discharge from the catheterization. In addition, each cardiologist kept a record of catheterizations he performed and complications that resulted.

Of 3,694 cardiac catheterizations performed during the 66-month period, 3,071 (83%) were performed as outpatient procedures. Ninety-eight percent of the procedures were performed using the Seldinger technique with Judkins-type preformed catheters; 79% of all patients had both right- and left-sided cardiac catheterization and coronary angiography. Most patients were men (Table I) with coronary artery disease (70.4%). Only 13.6% of all the patients studied had

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TABLE I Characteristics of Patients Undergoing Outpatient Cardiac Catheterization

Male	74.0%
Coronary artery disease (>50% stenosis)	70.4%
Valvular heart disease	12.5%
Congenital, cardiomyopathy	3.5%
Normal	13.6%
Total	100%

TABLE II Complications

Mortality	4	0.13%
Arrhythmia	13	0.42%
Myocardial infarction	2	0.07%
Vascular complications	11	0.35%
Neurologic complications	4	0.14%
Other	70	2.30%
No complications—discharged same day	2,967	96.59%
Total	3,071	100%

normal study results. Twenty-seven percent of all patients had 3-vessel disease, 32% had 2-vessel disease, 36% had 1-vessel disease and 5% had significant left main narrowing.

Complications (Table II): Thirty-four patients had significant complications (1.1%). Four patients died. One patient died in the cardiac catheterization laboratory after dissection of the left main coronary artery. This patient had severe 3-vessel disease and previous myocardial infarction. Anaphylactoid shock developed in 1 patient after left ventricular angiography and the patient could not be resuscitated. Two patients died outside of the cardiac catheterization laboratory. One patient suffered out-of-hospital cardiac arrest after he was discharged home. This patient had 2-vessel disease with a previous myocardial infarction and had been stable before, during and after the cardiac catheterization. His predischarge electrocardiogram and examination did not show any signs of ischemia or ventricular irritability. Another patient had a cerebrovascular accident during the procedure and died approximately a week later, secondary to complications related to the stroke.

Thirteen patients had significant arrhythmias requiring either treatment and/or admission to the hospital; 8 of these patients had ventricular tachycardia or ventricular fibrillation, which was successfully treated with lidocaine and or ventricular defibrillation. One patient with significant coronary artery disease had a cardiac arrest approximately 10 hours after discharge from the hospital. He was successfully resuscitated but did suffer long-term neurologic damage. The remaining patients had bradyarrhythmias, which responded to atropine or pacing. None of these patients had further complications.

Only 2 patients had a myocardial infarction within 24 hours after cardiac catheterization. Both patients recovered uneventfully. Eleven patients had vascular complications related to the procedure. Three patients were admitted 2 to 3 weeks after the catheterization for right groin abscesses and were treated with drainage and antibiotics. Six patients required admission after the catheterization for repair of femoral artery aneurysm or endarterectomy. One patient suffered a deep vein thrombophlebitis and 1 patient had an acute embolic episode to the contralateral femoral artery during the cardiac catheterization.

Four patients had a cerebrovascular accident. Two of these patients had only transient symptoms, which resolved completely within 24 hours. One patient who had a history of hypertensive disease for many years had a brain stem infarction during left ventricular angiography. This resulted in permanent residual neurologic damage. Another patient had a cerebrovascular accident during the procedure and died a week later. (This patient is listed as one of the 4 deaths.)

Seventy patients (2.3%) were admitted after the procedure for a variety of reasons, including severity of disease, hypotension, bleeding at the puncture site, vasovagal reactions, allergic reactions and social reasons. More than 96% of patients had no complications and were discharged the same day.

Discussion

The incidence of major complications of cardiac catheterization in previous studies has been well documented. Bourassa and Noble[1] reviewed 5,250 patients studied by the percutaneous femoral approach at the Montreal Heart Institute with a reported mortality rate of 0.23%, a nonfatal myocardial infarction rate of 0.09%, a vascular complication rate of 0.85% and a neurologic complication rate of 0.13%. Potentially serious ventricular arrhythmias were seen in 0.80% of cases. Thus, the total major complication rate in their study was 2.1%. Abrams and Adams[2] reviewed data compiled from a national survey of cardiac catheterization laboratories in 1975. A total of 89,079 patients underwent angiography by both the femoral and brachial methods. They found an average mortality rate of 0.15%, a myocardial infarction rate of 0.23% and cerebral embolism in 0.10% of patients studied by the femoral technique.

More recently, Davis et al,[3] in a collaborative study, prospectively analyzed the complications of coronary arteriography in 7,553 patients. The average mortality rate was 0.20% overall (0.14% femoral and 0.51% brachial procedure), nonfatal myocardial infarction occurred in 0.25% (0.22% femoral and 0.42% brachial), vascular complications in 0.70%, embolic episodes in 0.09% and ventricular fibrillation in 0.63%, yielding a total major complication rate of 1.87% (1.78% for the femoral approach). These studies have been the standard against which all cardiac catheterization laboratories must compare.

In an attempt to improve utilization of health care resources, outpatient cardiac catheterization has been initiated in many laboratories. Early reports from these laboratories suggested that the complication rate could be comparable to that seen with inpatient procedures.[4,5] The most detailed report on outpatient cardiac catheterization by the percutaneous femoral method comes from Mahrer and Eshoo.[6] His group reported on 308 patients and found a mortality rate of 0.30% and a major complication rate of 2.24%. Ninety-one percent of their patients were discharged the same day and 6.8% were admitted for observation. The incidence of major

TABLE III Complication Rates of Coronary Arteriography in Various Studies

1st Author	No. of Pts	Mortality (%)	MI (%)	Vascular (%)	CNS (%)	Arrhythmias (%)	Total (%)
Bourassa[1]	5,250	0.23	0.09	0.85	0.13	0.80	2.1
Abrams[2]	89,079	0.15	0.23	. . .	0.10	. . .	. . .
Davis[3]	7,553	0.20	0.25	0.70	0.09	0.63	1.87
Mahrer[6]	308	0.30	0.97	0.65	0.32	. . .	2.24
Present study	3,071	0.13	0.07	0.35	0.14	0.42	1.1

CNS = central nervous system; MI = myocardial infarction.

complications in our series (1.1%) compares favorably with both the inpatient and outpatient series previously reported (Table III). Our mortality rate of 0.13% is at least as good as or exceeds the reported rates. Ninety-six percent of our patients were discharged the same day of the procedure.

The 2 patients who had out-of-hospital cardiac arrest after discharge deserve further comment. One patient died and the other patient had permanent residual neurologic deficit as a consequence. Both patients had significant multivessel coronary artery disease, but were in stable condition before and after the procedure. Patients with serious coronary artery disease are at risk for major cardiac events such as myocardial infarction, arrhythmias or death as a result of the natural history of their disease. The incidences of such pseudocomplications occurring just before or within 24 hours after a planned but unperformed cardiac catheterization is reported to be 2.3%, including a death rate of 1.2%.[7]

Although there was a temporal relation to the cardiac catheterization in our 2 patients, it is difficult to determine a causal relationship. In addition, it is speculative as to whether or not the outcome of resuscitation might have been different if they had been inpatients. The incidence of this complication (0.065%) is well within the probability of natural occurrence for patients with cardiac disease.

In conclusion, the present study indicates that outpatient cardiac catheterization is safe and feasible and may reduce the cost of evaluation of cardiac disease.

Acknowledgment: We are indebted to the invaluable assistance of the technicians and nursing staff of the Cardiac Catheterization Laboratory at the Royal Alexandra Hospitals.

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Relation of Hemoglobin A_1 and Blood Glucose to Cardiac Function in Diabetes Mellitus

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To examine the relation of short- and long-term changes in glucose metabolism to cardiac function, radionuclide cineangiography and echocardiography were performed in 10 young insulin-dependent diabetic patients without clinical evidence of heart disease. Cardiac assessments were performed before and after both acute variations in blood glucose, and induction of chronic "tight glucose control" involving normalization of hemoglobin A_1 concentrations. In diabetic patients, left ventricular (LV) ejection fraction (EF) at normal blood glucose concentration was indistinguishable from values in 11 normal subjects. However, during hyperglycemia (about 300 mg/dl), the average EF at rest was 61%, significantly higher than that during normoglycemia (56%, $p < 0.001$). No significant change in LV diastolic dimension was noted in association with shifts between high and normal blood glucose concentrations. Normalization of hemoglobin A_1 was achieved within 6 to 25 weeks. This alteration had no significant effect on LVEF, mitral valve E-F slope, or the response of systolic function to blood glucose levels. In addition, no correlation was found between LVEF and hemoglobin A_1 concentrations in 4 of 5 evaluation periods. Thus, in young insulin-dependent diabetic patients without overt heart disease, variation in blood glucose concentration is associated with small but significant variation in EF at rest; normalization of hemoglobin A_1 has no significant effect on LVEF or the response of systolic function to blood glucose levels.

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The association between diabetes mellitus and clinically important cardiac disease has long been recognized, but the effects of acute and chronic control of glucose metabolism on cardiac function in the diabetic patient are not well defined. Although coronary artery disease is the most common cause of clinical cardiac debility in the diabetic patient,[1] clinical,[2–6] epidemiologic,[7] experimental[8,9] and autopsy data[2,10] suggest that primary myocardial dysfunction also may result from diabetes. However, both the existence of such a condition[11,12] and its relation to clinical control of glucose metabolism remain unclear. Many proteins are glycosylated in the poorly controlled diabetic patient,[13–15] and extrapolation from this observation[16–18] suggests that elevated blood concentrations of hemoglobin A_1, a glycoprotein indicator of the chronic (approximately 6 weeks) average blood glucose level,[13] may occur concomitantly with glycosylation reactions involving myocardial proteins. An excess of myocardial glycoproteins has been noted at autopsy in diabetic patients without other apparent heart disease and in animals with experimentally induced diabetes mellitus, and has been associated with diminution of both left ventricular (LV) compliance and systolic functional reserve.[2,8] Therefore, to assess prospectively the cardiac functional effects of both acute variations in blood glucose and of chronic "tight blood glucose control," defined as involving normalization of hemoglobin A_1, we performed radionuclide cineangiography and echocardiography in 10 young diabetic patients without clinically apparent cardiomyopathy.

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Methods

Ten patients (7 men and 3 women), aged 21 to 30 years, with insulin-dependent diabetes mellitus were studied. No patient had evidence of coronary artery or other cardiac disease, and none had a systemic disorder other than diabetes that might affect the heart. The mean duration of known diabetes was 7 years (range 3 weeks to 18 years). All patients were within 20% of ideal body weight. Two patients had proliferative diabetic retinopathy. All patients were receiving insulin therapy before and during the study. Before the study, all patients had normal blood urea nitrogen and creatinine levels.

The study design is depicted in Figure 1. Patients were admitted to the Clinical Research Center; morning insulin was withheld until the blood glucose level was elevated to approximately 300 mg/dl. Baseline noninvasive assessment of cardiac function was then undertaken (C_1). After initial determinations, closed-loop insulin therapy (see later) was

carried out during a 4-hour period to bring blood glucose levels into normal range, approximately 80 mg/dl. Examination of LV function was then repeated (C_2). Closed-loop insulin therapy was used to maintain normoglycemia until the next morning, when LV function again was assessed (C_3). The patients were then discharged from the hospital, and treated with insulin therapy using home glucose monitoring (see later). This regimen was continued for at least 6 weeks, until chronic normoglycemia had developed as indicated not only by patient-monitored glucose determinations but also by normalization of hemoglobin A_1. Patients were readmitted for noninvasive cardiac assessment while normoglycemic (C_4). Insulin was withheld for 4 hours, permitting blood glucose levels to rise with administration of a glucose load, again to approximately 300 mg/dl, at which point the final cardiac assessment was undertaken (C_5). The direction of acute alteration in blood glucose was reversed (high to normal vs normal to high) at C_1, C_2 vs C_4, C_5 to eliminate potential methodologic bias or diurnal influences in assessing the effects of such alterations. All cardiac assessments were performed approximately 3 hours after meals.

Two methods of closed-loop insulin therapy were used to achieve rapid alterations in blood glucose concentration. During the first hospitalization between C_1 and C_2, 7 patients were treated using an artificial endocrine pancreas (Biostator®, Life Science Instruments). To eliminate potential saline load effects that may accompany use of the Biostator, in-hospital manipulation of blood glucose was achieved at all other times by a "manual closed-loop system," consisting of fingerstick blood glucose determinations and administration of either intravenous insulin or oral glucose loads.

Outpatient insulin therapy consisted of a previously described split-dose sliding scale insulin regimen and home glucose monitoring system[19] to effect normalization of hemoglobin A_1.

At each cardiac assessment (C_1 to C_5), Biostator plasma glucose readings or reflectance colorimeter blood glucose determinations[19] were performed and were confirmed by assessment of plasma glucose by standard techniques. Plasma glucose measurements are approximately 15% higher than blood glucose determinations (to which all plasma glucose measurements were converted).

Chronic "blood glucose control" was assessed by determination of hemoglobin A_1 levels at weekly intervals. Blood samples were saline-incubated according to the method of Goldstein et al[20] to minimize effects of acute blood glucose changes on hemoglobin A_1 measurements, and were chromatographed the following day. Total glycosylated hemoglobin was determined in triplicate by ion exchange chromatography using a prepacked microcolumn (Quik-Column,® Helena Laboratories). Follow-up cardiac evaluation was performed when the final hemoglobin A_1 concentration was within normal range (5.9 to 8.9%). Initial and final (post-treatment) hemoglobin A_1 concentrations used in analysis were each the average of 3 separate determinations made within a period of 2 weeks.

Noninvasive cardiac evaluation at each assessment point (C_1 to C_5) included M-mode echocardiography at rest and radionuclide cineangiography performed at rest and exercise as indicated in Figure 1. Echocardiographic determinations were made using standard techniques and measurement criteria.[21] LV diastolic dimension (DD) and mitral valve E to F slope (MVEFS) were determined as the mean of measurements from 3 consecutive cardiac cycles. Gated equilibrium radionuclide cineangiography, using technetium-99m-labeled red cells, was carried out with the patient at rest in the modified left anterior oblique[22] and right anterior oblique positions, and during maximal symptom-limited supine bicycle exercise in the modified left anterior oblique position. Data were collected by methods analogous to those previously described.[22–24] After images and time-activity curves were obtained with the patient at rest, bicycle ergometry was begun at a load of 25 W, with increments of 25 W at 2-minute intervals. Exercise was continued at assessment C_1 until fatigue or dyspnea prevented further exercise; at subsequent exercise studies, exercise was continued until the patient had reached an external workload and heart rate indistinguishable from that at C_1. This endpoint generally was also associated with limiting dyspnea or fatigue. Imaging always included the final 2 minutes of exercise.

Radionuclide cineangiographic data obtained in the diabetic patients were compared with data obtained in 11 age-matched normal volunteers (10 men and 1 women, aged 19 to 30 years) without clinical, electrocardiographic or echocardiographic evidence of cardiac abnormalities. Previous studies in large groups of normal subjects in our laboratories, including subjects aged 19 to 30 years, have indicated that LV ejection fraction (EF) varies between 45 to 75% when such subjects are at rest, and that during exercise to heart rates of 110 beats/min or higher (the range achieved in our diabetic patients), EF invariably exceeds 54%, and increases at least 5% during exercise.[25,26]

Data are expressed as mean ± standard error of the mean. Statistical assessments were performed with Student t tests for paired and unpaired data (as appropriate) and with linear regression analysis.[27] "Multiple look" bias theoretically may affect conclusions based on this approach because one can generally expect that 1 in 20 p values will be <0.05 when no difference exists. However, the highly statistically significant differences (<0.001) noted among results obtained at different assessment points in the protocol quantitatively indicate that these differences can be expected to be real.

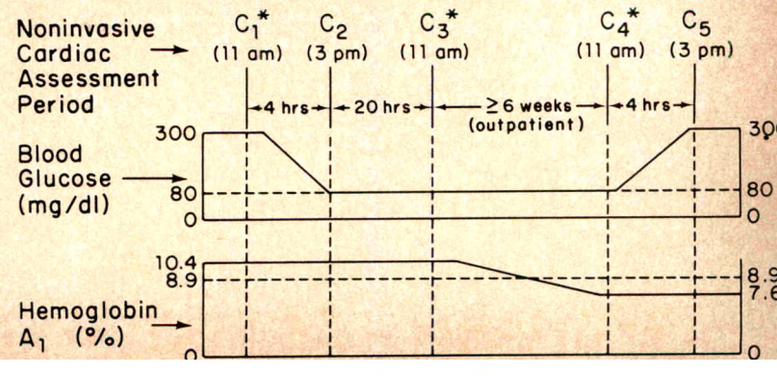

FIGURE 1. Study design. Diabetic patients progressed sequentially (**left** to **right**) through the noninvasive cardiac assessments. The state of glucose metabolism control was therapeutically altered in accordance with the upper and lower diagrams, which represent blood glucose and hemoglobin A_1 levels, respectively. Normal hemoglobin A_1 is less than 8.9%. C_1 to C_5 = cardiac assessment periods. *When radionuclide cineangiography was performed both at rest and during exercise.

Results

The results of manipulation of blood glucose are shown in Figure 2. Hemoglobin A_1 concentrations were supernormal at baseline in 9 of 10 patients. Average hemoglobin A_1 decreased from 10.4 ± 0.5% to 7.6 ± 0.2% ($p < 0.001$) after a period of 6 to 25 weeks of outpatient insulin therapy. Moderate hyperglycemia was achieved at cardiac assessments C_1 and C_5 and the average blood glucose level was less than 100 mg/dl at all other assessments.

At each evaluation (C_1 to C_5), none of the 10 patients demonstrated regional LV dysfunction. Moreover, when blood glucose levels were within normal range, mean EF values for patients were statistically indistinguishable from those of normal subjects (Fig. 3). All patients had a normal increase in EF with exercise at each of the 3 assessments in which exercise was performed. No significant changes in heart rate and blood pressure were noted at different assessment points (C_1 to C_3).

However, a small but significant variation in EF at rest was noted in association with variation in blood glucose (Fig. 4). During hyperglycemia, average EF at rest was significantly higher than during normoglycemia. This relation was present when C_1 values were compared with those obtained after either 4 or 24 hours of therapy. EF during exercise did not vary significantly with blood glucose changes (exercise EF C_1 = 74 ± 3, EF C_3 = 72 ± 3%, difference not significant [NS]). After normalization of hemoglobin A_1, the variation of EF at rest with blood glucose again was noted (Fig. 4), although the sequence of glucose alterations was reversed as compared with C_1, C_2.

Achievement of chronic blood glucose control, as indicated by the normalization of hemoglobin A_1, had no significant effect on EF at rest, either during normoglycemia or during hyperglycemia (Fig. 4), or during exercise (exercise EF C_4 = 72 ± 4%, NS vs C_3). Moreover, regardless of blood glucose concentration, no significant correlation existed between hemoglobin A_1 and EF at rest except for rest EF C_3 where the correlation coefficient ($r = -0.70$) reached minimal statistical significance ($p < 0.05$). No significant correlation existed between hemoglobin A_1 and EF during exercise at any evaluation period.

Echocardiographic assessment revealed no significant difference between average LVDD when blood glucose was normal (LVDD C_2 = 4.7 ± 0.2 cm) and when blood glucose was elevated (LVDD C_1 = 4.8 ± 0.1 cm [NS vs C_2]). Moreover, during all assessments of the diabetic patients, LVDD was within the range measured in normal subjects. In addition, no significant change in LVDD resulted after normalization of hemoglobin A_1 (LVDD C_4 = 4.8 ± 0.2 [NS vs C_2], C_5 = 4.8 ± 0.2 cm [NS vs C_1]). Thus, the decrements in LVEF manifested on normalization of blood glucose occurred without echocardiographic evidence of significant LV diastolic volume change.

Echocardiographic assessment of MVEFS showed that although 2 patients manifested subnormal MVEFS (less than 50 mm/s) before outpatient therapy, values for all patients were virtually unchanged after normalization of hemoglobin A_1 (MVEFS C_1 = 64.9 ± 6.0, C_5 = 68 ± 6.0 mm/s, NS) or acute shifts in blood glucose

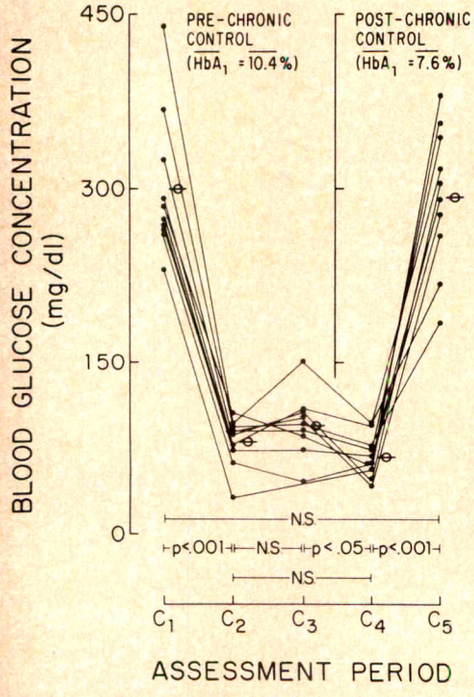

FIGURE 2. Blood glucose concentration at each cardiac assessment period both before and after normalization of hemoglobin A_1 (CHRONIC CONTROL). One patient did not undergo cardiac assessment at C_3. Θ = average values; C_1 to C_5 = cardiac assessment periods; HbA_1 = average hemoglobin A_1; N.S. = not significant.

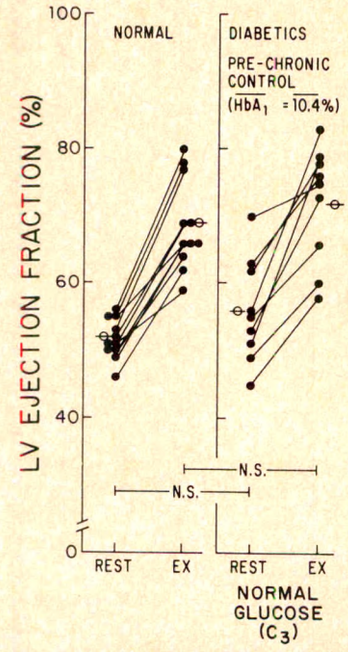

FIGURE 3. Effect of maximal exercise (EX) on left ventricular (LV) ejection fraction in normal subjects, and in diabetic patients during assessment period C_3, when the blood glucose level was normal (mean blood glucose 94 mg/dl). Abbreviations as in Figure 2.

(MVEFS C_2 = 73 ± 6.0 [NS vs C_1], C_4 = 65 ± 7.0 mm/s [NS vs C_5]). Thus, no change in this index of LV compliance[28] was detected during the interventions used.

Discussion

Patients with diabetes mellitus frequently manifest clinical evidence of cardiac disease, primarily in association with abnormalities of the coronary arteries.[1] Evidence for a "diabetic cardiomyopathy" in the absence of coronary disease has only recently accumulated,[2–10] and its existence, pathogenesis and clinical importance remain controversial.[11,12] Further, the capacity for modification of LV function in the diabetic patient by shifts in blood glucose and insulin concentrations (which substantially modify cardiac metabolism[18] and may cause glycosylation of myocardial proteins[16–18] with resultant alteration in cardiac structure and function[2,8]) is poorly understood.

Our findings indicate that moderate hyperglycemia in the young diabetic patient is associated with a small increase in LVEF at rest compared with results obtained in the normoglycemic state. This relation between EF and blood glucose is not mitigated by chronic tight glucose control involving normalization of hemoglobin A_1, and it is not clear which of many mechanisms may explain such an effect. Although echocardiographic measurements suggested that no significant alteration in end-diastolic volume occurred in association with acute changes in blood glucose, we cannot preclude the possibility that small volume shifts may have occurred, undetected by our methods, changing EF in accordance with the Frank-Starling relation. Also, high concentrations of blood glucose, like mannitol, exert osmotic effects that can alter cardiac function by dilating resistance vessels, increasing coronary blood flow,[29] causing autonomically mediated responses[30] and enhancing inotropic state.[31] Moreover, in diabetic patients, changes in the relative amounts of glucose and insulin exert complex effects on glucose utilization, adenosine triphosphate levels, and β oxidation of free fatty acids, which may also result in alterations in contractile function.[18]

Our results suggest that acute changes in glucose metabolism can cause small but significant modification of cardiac function in the diabetic patient. The association of blood glucose and EF may be of clinical importance. Evaluations of LV function in patients with diabetes mellitus should be performed with the knowledge that the blood glucose at the time of testing may affect results. Whether acute changes in blood glucose and resultant small changes in cardiac function are of significance for the diabetic patient with heart disease would appear to be dependent on the mechanism by which glucose acts on the myocardium, and requires further direct study for elucidation.

Our results indicate that normalization of hemoglobin A_1 in young diabetic patients without cardiac symptoms has no significant effect on systolic or diastolic LV performance. Other investigators show that accumulation of interstitial glycoprotein occurs in the myocardium in chronically uncontrolled diabetes and is associated with altered ventricular compliance.[2,8] Our findings are consistent with these earlier results in that 2 patients manifested clearly subnormal echocardiographic E-F slope, and the group as a whole evidenced an average value near the lower end of the normal range. Echocardiography provides only an estimate of diastolic function[28] and more sensitive indexes may be required to detect alterations in diastolic function caused by altered glucose levels.

Although our data failed to show a significant relation between chronic glucose control and cardiac function, conclusions based on these data must be guarded. Previous investigations suggest that diabetic women, and patients with diabetic retinopathy or nephropathy,[4,7] appear most likely to manifest cardiomyopathic findings. Only 3 women and 2 patients with proliferative retinopathy were included in our study group, and at baseline none of our patients manifested subnormal systolic function and only 2 evidenced diastolic dysfunction. Thus, the paucity of detectable preexisting systolic and diastolic abnormalities may have precluded observation of a significant effect of hemoglobin A_1 normalization. Also, although myocardial protein degradation is increased in diabetic rats,[32] the rate of acquisition or turnover of glycosylated myocardial proteins is not known. Therefore, longer periods of improved diabetic control, more sensitive techniques, or assessment of a different diabetic patient population, might possibly have provided different results. Further study is needed to clarify these points.

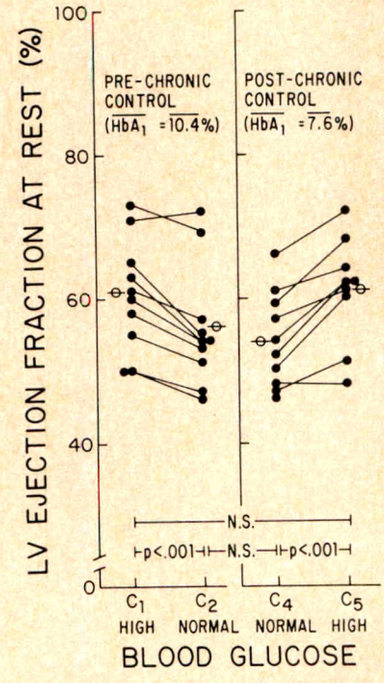

FIGURE 4. Effect of blood glucose concentration on systolic left ventricular (LV) performance at rest in diabetic patients as determined by ejection fraction. Results of cardiac evaluation at C_5 were not obtained in 1 patient because of technical difficulties. HIGH = approximately 300 mg/dl; NORMAL = approximately 80 mg/dl; other abbreviations as in Figure 2.

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Electrophysiologic Evaluation of the Cardiac Conduction System and Its Autonomic Regulation in Familial Amyloid Polyneuropathy

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A high incidence of cardiac conduction disturbances is a salient feature in familial amyloid polyneuropathy (FAP) and amyloid infiltration of the conduction system has been found. In patients with FAP autonomic nervous dysfunction involving gastrointestinal, urogenital and cardiovascular systems has been described. However, the present study is the first to evaluate the results of autonomic tests and pharmacologic intervention in the autonomic nervous regulation of the cardiac conduction system during an invasive electrophysiologic study. Seven patients with FAP and severe disturbances of the conduction system, evaluated concerning indications for pacemaker treatment, were studied; in 3 of them the parasympathetic regulation was found to be abolished. In 1 patient the observations indicated either vagal overactivity or denervation oversensitivity of the receptors. The function of the β adrenoceptors was intact in all patients, but a disturbance of sympathetic innervation could not be excluded. Dysfunction of autonomic nervous regulation of the cardiac conduction system was thus found in 4 of 7 patients. However, most conduction abnormalities were irreversible, indicating amyloid infiltration of the conduction system as the predominant pathophysiologic mechanism, in accordance with the findings of pathoanatomic studies.

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Familial amyloid polyneuropathy (FAP) is characterized by generalized amyloidosis and sensorimotor and often also autonomic neuropathy.[1] Amyloid deposits have been demonstrated in the myocardium as well as in all parts of the conduction system in patients with FAP,[2,3] and atrioventricular conduction disturbances[4–6] and sinus node dysfunction[7] are important clinical manifestations. At least 10% of Swedish patients with FAP require permanent pacemaker therapy.[8] In a previous report the presence of autonomic neuropathy of the heart was suggested, but the function of the sinus node was not evaluated, leaving the question of the site of the dysfunction unanswered.[9] An electrophysiologic study on Japanese patients has been reported, which was not designed, however, to test the autonomic regulation.[10]

The purpose of the present study was to investigate the cardiac conduction system and its autonomic nervous regulation in patients with FAP.

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Methods

Seven patients, representing approximately 10% of the Swedish patients with FAP who are alive, were examined. All of them had a typical clinical picture and rectal or skin biopsy verified amyloidosis. Heart biopsies were not performed. Indirect evidence of cardiac amyloidosis was obtained from standard electrocardiograms in all patients, echocardiograms in all but patient 6 and heart scintigrams in patients 1 and 3 (Table I). As no other cause of heart disease was found, the New York Heart Association criteria of cardiac amyloidosis were fulfilled.[11]

The main electrocardiographic diagnosis was atrioventricular block of varying degree in patients 1, 2, 3, 4 and 5 and sinus node dysfunction in patients 6 and 7, in the latter case combined with atrial flutter. They had all experienced symptoms that could be attributed to bradyarrhythmias, except patients 4 and 7, and the electrophysiologic study was part of the evaluation for pacemaker therapy.

Functional classification (Table I): A 4-grade classification of the severity of the polyneuropathy has been presented previously.[12] This is essentially equivalent to the recommendations of the New York Heart Association for classification of cardiac functional status,[13] which were also applied in this study, except in patient 1, with the most severe degree of polyneuropathy.

Analysis of electrocardiographic recordings: Definitions and terms related to cardiac rhythm follow the recommendations of Hecht et al[14] and Robles de Medina et al.[15] Long-term electrocardiographic recordings of a duration of at least 24 hours were analyzed both automatically and manually.

TABLE I Clinical Data and Functional Classification of Seven Patients with Familial Amyloid Polyneuropathy and Cardiac Conduction Disturbances Investigated Electrophysiologically

Pt	Age (yr) & Sex	Duration of Polyneuropathy (yr)	Degree of Polyneuropathy	Cardiac Function (NYHA class)	Cardiomegaly	Echo	Cardiac Scintigram
1	49F	16	++++	—	0	Typical	Typical
2	67F	5	+++	II	+	Typical	Normal
3	60M	6	++	III	+	Typical	Typical
4	66M	7	++	I	0	Typical	...
5	42F	7	++	II	0	Typical	...
6	49F	16	+++	II	0	Normal	...
7	65F	7	++	II	+	Typical	...

Echo = echocardiogram; NYHA = New York Heart Association; + = present; 0 = absent; ... = not performed.

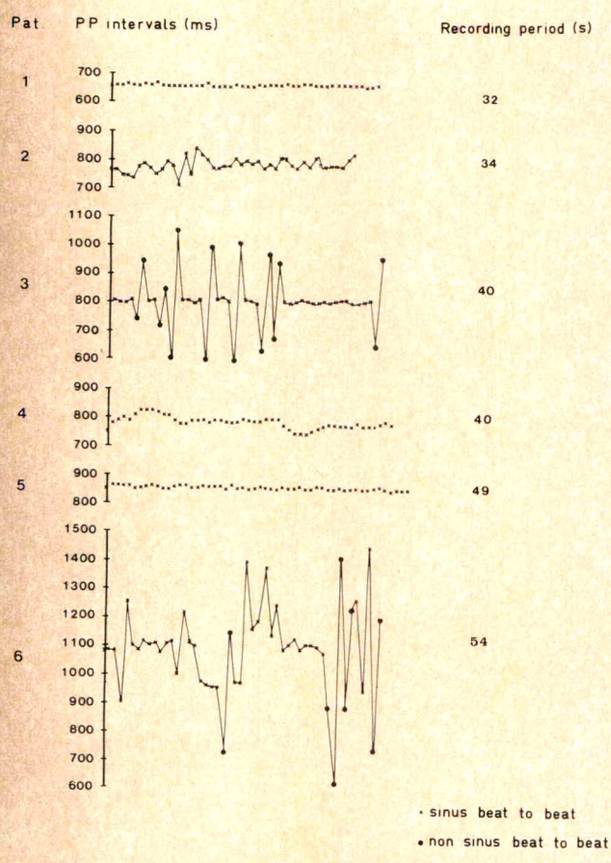

FIGURE 1. Spontaneous variations in atrial activity recorded during the electrophysiologic study—consecutive PP intervals. Patient 1—minimal variations in sinus node activity, implying lack of vagal influence, consistent with the absence of response to carotid sinus pressure and atropine injection. Patient 2—beat-to-beat variations within reference limits,[22] but of an unsystematic kind, which may be due to the sinus node dysfunction. Patient 3—pronounced beat-to-beat variations resulting in nodal extrasystoles with compensatory pauses. Sinus node activity with minimal variations consistent with the lack of response to carotid sinus pressure and atropine injection. Patient 4—variations in sinus node activity in a continuous undulating mode within reference limits, consistent with normal sinus node function and normal responses to carotid sinus pressure and atropine injection. Patient 5—minimal variations in sinus node activity, implying impaired vagal function, consistent with the absence of response to carotid sinus pressure and the minimal response to atropine injection. Patient 6—increased sudden variations in sinus node activity occurring in a haphazard way, possibly reflecting the sinus node dysfunction. Even greater variations due to ectopic supraventricular beats are seen. Patient 7—had constant atrial flutter.

Other investigative procedures: Echocardiographic examination was performed according to the routine procedure and amyloid infiltration was diagnosed in the presence of hyperrefractile echoes and left ventricular hypertrophy.[16–18]

Heart scintigrams were recorded and interpreted by procedures described previously. A pattern that is typical, although not completely specific, for FAP has been described[19] and was found in patients 1 and 3.

Electrophysiologic study: The patients were in the nonsedated, postabsorptive state during the investigation. Pharmacologic treatment known to affect the cardiac conduction system was withheld for more than 5 half-lives before the investigation, at which time no measurable amounts were found in blood samples. All patients had given their informed consent and the investigation protocol was approved by the Medical Ethics Committees of the hospitals.

Two No. 6Fr electrode catheters with a 1-cm interelectrode distance were introduced percutaneously under local anesthesia through a femoral vein. A quadripolar catheter was positioned high in the right atrium against the lateral wall for simulation and recording. A tripolar electrode catheter was positioned across the tricuspid valve for recording of low atrial activity and the His bundle potential. The intracardiac electrogram and surface leads I, II, V_1 and V_6 were continuously recorded on a multichannel Mingograph (Siemens-Elema) with frequency limits of 50 and 700 Hz at a paper speed of 100 mm/s. Pacing was performed with a stimulus duration of 2 ms at a voltage of 2 to 3 times the stimulation threshold, using a stimulator for programmed pacing (Devices Ltd).

Investigation protocol: Recordings of spontaneous heart rhythm and conduction intervals were first obtained in the basal state and later analyzed for beat-to-beat variations of sinus node activity (Fig. 1).

Carotid sinus pressure was then applied for 2 periods of 10 seconds on each side. PP and AH intervals were measured as the average of at least 5 and 3 intervals, respectively, immediately before and during carotid sinus pressure.

The sinus node recovery time was determined by atrial pacing for periods of 10 seconds (3 times) and 30 seconds (2 times) at atrial rates of 90 and 130 beats/min. The longest recovery time was chosen and corrected for heart rate by subtracting the mean of 5 PP intervals immediately before the pacing period.

The paced atrial rate at Wenckebach block was determined by incremental pacing, with increments of 10 impulses per minute (ipm)/10 seconds, starting at a rate slightly above the resting rate. The refractory period of the atrioventricular node was determined by delivering 1 atrial extrastimulus at decreasing intervals coupled to a 5-second period of regular pacing at 100 ipm or the highest possible rate below 100 ipm.

TABLE II Conduction Intervals and Results of Sinus and Atrioventricular Nodal Functional Tests Before and After Inhibition of Autonomic Tone by Atropine and Propranolol

	PP (ms)		RR (ms)		HR (beats/min)		PQ_{II} (ms)		PA (ms)		AH (ms)	
Pt	B	ATI	B	ATI	B	ATI	B	ATI	B	ATI	B	ATI
1	670	1,185	670	1,185	90	51	170	180	25	25	70	95
2	765	680	1,055	680	57	88	430	465	50	60	315	335
3	805	665	805	665	74	90	225	200	85	85	60	85
4	800	640	800	640	75	94	255	220	65	70	105	95
5	845	760	845	760	71	79	225	240	45	50	135	155
6	1,170	1,095	1,170	1,095	51	55	195	290	45	45	115	110
7*	265	...	955	...	63	...	...	...	...	...	...	...
Mean	843	838	900	838	69	76	250	266	53	56	133	146
Normal value[21] (Mean ±2 SD)	600–1,200	625–930	600–1,200	625–930	50–100	65–100	120–200	120–200	25–65	35–65	50–105	50–100

	HV (ms)		QS_{II} (ms)		SRT (ms)		CSRT (ms)		ERP-AVN (ms)		Wenckebach Rate (beats/min)	
	B	ATI	B	ATI	B	ATI	B	ATI	B	ATI	B	ATI
1	40 + 25†	35 + 25	100	95	955	2,385	250	1,265	<230	<240	167	130
2	55	55	125	130	1,445	1,420	645	680	660	720	90	85
3	75	75	120	125	1,180	1,260	415	555	530	620	98	85
4	65	65	150	155	1,235	1,080	415	385	410	380	138	135
5	45	45	95	95	1,260	1,310	375	350	580	600	97	100
6	30	35	100	95	1,400	>6,400	365	>4,000	430	...‡	118	...‡
7	55	...	140	...	...	...	...	...	...	...	...	...
Mean	56	56	119	116	1,246	2,309	411	1,206	473	512	118	107
Normal value[21] (Mean ±2 SD)	20–60	25–55	<120	<120	900–1,735	735–1,420	200–545	70–505	170–420	185–385	>130	>130

* Atrial flutter; † Split His potential; ‡ Long asystoles after atrial pacing for SRT.

AH = atrioventricular nodal conduction interval; ATI = autonomic tone inhibition; CSRT = corrected sinus node recovery time; ERP-AVN = effective refractory period of the atrioventricular node; HR = heart rate; HV = His-Purkinje conduction interval; PA = atrial conduction interval; PQ_{II} = atrioventricular conduction interval, lead II; QS_{II} = duration of ventricular complex, lead II; SD = standard deviation; SRT = sinus node recovery time; ... = not performed.

TABLE III Summary of Tachyarrhythmias and Conduction System Abnormalities in Seven Patients with Familial Amyloid Polyneuropathy. Results Obtained from Standard Electrocardiograms, Long-Term Electrocardiographic Recordings and Electrophysiologic Studies

Pt	SN	AVN	HB	RBB	LAF	LPF	AVB Degree	APC	VPC	SVT	VT	Pacemaker Therapy
1	+*	0	+*	+*	+	(+)*	I, III	0	0	0	0	+
2	+	+*	0	0	(+)	(+)	I, II	+	+	0	0	0
3	+	+	+*	+	+	0	I, II	0	+	0	+	+
4	0	0	+*	0	+	+	I	+	+	0	0	0
5	+	+	0	0	0	0	I, II	0	+	+	0	+
6	+	+*	0	0	+	0	–	0	0	0	0	+
7	+	0	0	(+)*	+	+*	–	0	0	+	0	+

* Information obtained only during the electrophysiologic study. Parentheses indicate atypical or intermittent.
APC = atrial premature complex; AVB = atrioventricular block (first-, second-, or third-degree); AVN = atrioventricular node; HB = bundle of His; LAF = left anterior fascicle; LPF = left posterior fascicle; RBB = right bundle branch; SN = sinus node; SVT = supraventricular tachycardia; VPC = ventricular premature complex; VT = ventricular tachycardia; + = abnormality present; 0 = normal.

It was defined as the longest nonconducted extrastimulus interval.

Isoproterenol, 0.1 μg/kg body weight, was then given intravenously (i.v.) over 30 seconds. The maximal heart rate[20] and the change in heart rate was determined.

Atropine, 0.02 mg/kg body weight, was given i.v. over 30 seconds when the heart rate had returned to the level before isoproterenol or when 20 minutes had elapsed. PP and AH intervals, the atrial rate at Wenckebach block and the refractory period of the atrioventricular node were determined before and after atropine administration.

Propranolol, 0.1 mg/kg body weight, was given i.v. over 30 seconds as soon as possible and usually 10 minutes after the atropine injection. All aforementioned conduction intervals and functional tests were then repeated during this pharmacologic inhibition of autonomic tone.

Statistical methods: A Student *t* test for paired observations was used to compare results obtained under different conditions, with a significance level of $p < 0.05$.

Results

The conduction intervals, uncorrected and corrected sinus node recovery times, atrioventricular nodal refractory periods and atrial rates at Wenckebach block recorded with the patients in the basal state and after inhibition of autonomic tone by atropine and propranolol are presented in Table II. Patient 7 had atrial flutter, which could not be terminated.

In summary, most patients had widespread involvement of the conduction system, and 5 received pacemaker treatment (Table III).

Interference with parasympathetic regulation of the heart (Table IV, Fig. 1): The comparison of data obtained during different conditions did not show any general significant difference, but there were great interindividual differences.

Parasympathetic stimulation by carotid sinus pressure did not cause any changes in PP or AH intervals in patients 1, 3 and 5, and *parasympathicolysis* with atropine had no effect or only a minimal effect on sinus nodal and atrioventricular nodal function. Figure 1 shows minimal variations in sinus node activity in the same patients. These results were probably a result of severely impaired or abolished vagal regulation of the cardiac conduction system. In the other patients carotid sinus pressure or atropine, or both, induced changes, indicating residual vagal influence on impulse formation

Patient 2 had sinus rhythm in the basal state, with first- and second-degree atrioventricular block in the atrioventricular node. Both atropine and isoproterenol abolished second-degree atrioventricular block and normalized the atrioventricular nodal refractory period and the Wenckebach rate.

Interference with sympathetic regulation of the heart: The heart rate response to isoproterenol was normal in all patients, with a rate increase to more than 90 beats/min.[20] The average increase in heart rate was 76% (range 30 to 155%, $p < 0.01$). A comparison between the measurements in the basal state and after administration of isoproterenol and atropine/propranolol showed that the β receptors of the conduction system in all patients reacted to β stimulation as well as to β blockade.

Discussion

It has been proposed that FAP may involve the autonomic nervous system,[7] and de Freitas et al[9] suggested that defective autonomic regulation of the heart may occur, but in their study the function of the cardiac conduction system was not evaluated.[9]

In a recently reported study,[10] 8 Japanese patients with FAP were investigated electrophysiologically. Two had prolonged sinus node recovery time. Wenckebach block occurred at low atrial rates, between 77 and 120 ipm in all 8, of whom 4 also had prolonged refractory period of the atrioventricular node; 3 had an HV interval exceeding 60 ms. Isoproterenol (continuous i.v. infusion, 0.5 μg/min) improved impulse formation and conduction as expected. However, atropine (1 mg i.v.), unexpectedly impaired sinus nodal and atrioventricular nodal function in most of their patients, which was not observed in our patients. Neither parasympathetic stimulation nor β-receptor blockade was attempted and no conclusions could be made concerning the cardiac innervation.[10]

The present study is the first to combine evaluation of the function of the cardiac conduction system and its autonomic regulation in FAP patients, and the first to unequivocally show autonomic neuropathy of the heart. The advantages of performing tests on autonomic heart regulation during an electrophysiologic study rather than during a conventional standard

TABLE IV Interference with Vagal Regulation of the Heart

Parasympathetic (Vagal) Stimulation
Carotid Sinus Pressure (CSP) Compared with the Basal (B) State

Pt	PP (ms)			AH (ms)			Vagal Activation
	B	CSP	Δ ± %	B	CSP	Δ ± %	
1	670	670	±0	70	70	±0	0
2	845	920	+9	320	340	+6	+
3	810	810	±0	60	60	±0	0
4	850	1,625	+91	115	225	+96	+
5	850	850	±0	140	140	±0	0
6	1,010	1,115	+10	110	115	+5	+
7	Atrial flutter; no change in blocking ratio						
Mean	839	998		136	158		
Reference[21]	600–1,200	567–1,741		—	—		

Parasympathicolysis (Vagolysis)
Atropine (A) Compared with the State Before (B) Atropine Administration

	PP (ms)			AH (ms)			ERP-AVN (ms)			Wenckebach Rate (beats/min)		
	B	A	(± Δ%)	B	A	(± Δ%)	B	A	(± Δ%)	B	A	(± Δ%)
1	635	600	+4	80	80	±0	230	220	−4	167	164	−2*
2	670	605	−10	320	275	−14	660	410	−38	87	128	+47†
3	640	640	±0	110	110	±0	530	510	−4	98	103	+5*
4	770	575	−25	110	80	−27	410	270	−34	140	146‡	+4†
5	710	710	±0	145	150	+3	580	560	−3	102	102	±0*
6	915	840	−8	100	110	+10	430	360	−16	136	138	+1†
7	Atrial flutter; increased proportion of conducted F waves resulting in increased heart rate											
Mean	723	662		144	134		473	388		122	130	

* Minimal vagolysis; † Vagolysis; ‡ Stopped when difference was clear.
Abbreviations as in Table II.
Patients 1, 3 and 5: changes less than ±5%, mean ±1%; patients 2, 4 and 6: changes between +95% and −40%, mean ±25%.

Functional evaluation of the whole conduction system was possible and the ability of the heart to respond to autonomic stimuli could thus be assessed. (2) The origin of spontaneous atrial activity could be accurately defined (patient 3, Fig. 1). (3) Three measures of atrioventricular nodal function were obtained: conduction time (AH interval), atrioventricular nodal refractory period, and atrial rate at Wenckebach block. All of them are influenced by autonomic nervous activity, like the PP interval, which, often is the only variable recorded in connection with autonomic tests.

The tests we used require comment: (1) Carotid sinus pressure is difficult to standardize, and dysfunction at any site along the reflex arc may cause an abnormal or absent response. (2) Atropine acts on the neuroeffector junction, and improvement of sinus nodal and atrioventricular nodal function after atropine administration must therefore be interpreted as an antagonism of preexisting vagal activity. (3) The normal spontaneous beat-to-beat variations depend on complex brain stem reflexes, with respiration as the main stimulus, and require an intact vagal system.[22] The results of these 3 different tests on parasympathetic function were concordant in all patients investigated (Table IV, Fig. 1). The results recorded in patients 1, 3 and 5 therefore indicate vagal denervation in a functional sense, but whether the dysfunction was neural or receptor, or both, cannot be stated.

We could not determine whether the parasympathetic dysfunction was paralleled by sympathetic nervous dysfunction in the same patients. However, in contrast to the results of the Portuguese study,[9] we did not find any hyporesponsiveness of the cardiac β adrenoceptors to isoproterenol, which we gave in the double dose. The reactions to propranolol were also as expected. Therefore, dysfunction at the β-adrenoceptor level apparently can be ruled out, although sympathetic neuropathy cannot be excluded.

From the *quantitative* point of view, the dysfunction of autonomic heart regulation in the present group of patients did not play a major role in conduction abnormalities, which were unaffected by pharmacologic intervention except in patient 2, in whom atropine improved atrioventricular nodal conduction. The partially reversible impairment of atrioventricular nodal function in this patient could be a result of increased vagal activity, owing to nervous excitation in analogy with paresthesias, or a result of denervation oversensitivity of the receptors.

The main pathophysiologic mechanism underlying the conduction abnormalities in our patients with FAP apparently is *amyloid infiltration* of the conduction system, in accordance with histopathologic studies.[2,3]

The disease was fairly advanced in all cases. However, the normal findings in regard to vagal function in patient 4 suggest that the vagal function may remain intact

despite fairly advanced cardiac amyloidosis. The same apparently applies to β adrenoceptors.

FAP is a rare disorder, but the combination of myocardial disease and autonomic dysfunction is also found in patients with diabetes mellitus. Therefore, a warning should be extended concerning the interpretation of heart rate reactions in autonomic tests to include diabetic patients. An electrophysiologic study may be required both in patients with FAP and in diabetic patients for assessment of the ability of the cardiac conduction system to respond to different autonomic tests.

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Atrial Septal Aneurysm: Echopolycardiographic Study

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Atrial septal aneurysm (ASA) with diagnosis during life is a rarely reported anomaly, especially when not associated with other congenital or acquired valvular cardiopathies. Among 4,000 routine echocardiograms, 23 cases of ASA were found (8 men and 14 women, aged 19 to 79 years). Three patients had coronary artery disease, 2 had dilated cardiomyopathy, 2 had systemic hypertension, 11 had mitral valve prolapse and 5 had no other identifiable cardiovascular diseases. Echocardiography revealed various motion patterns of ASA. No phonomechanocardiographic findings were related to the presence of ASA, and no correlation between echographic and phonocardiographic findings was found.

(Am J Cardiol 1985;56:653–656)

Although atrial septal aneurysm (ASA) is a well known morphologic phenomenon,[1] it has been reported as an unexpected finding during autopsy,[1–9] angiographic examinations[10–15] and, more recently, echocardiographic examinations.[16–29] ASA is rarely diagnosed in living patients, particularly when it is not associated with other congenital or acquired valvular cardiopathies. The present report describes the echo-phonocardiographic findings of 23 adult patients with ASA.

Methods

Twenty-three patients among 4,000 consecutive patients examined were found to have ASA by echocardiography. Clinical and instrumental data are listed in Table I. Three patients had coronary artery disease, 2 had dilated cardiomyopathy, 2 had systemic hypertension, 11 had mitral valve prolapse (2 of whom also had systemic hypertension and 2 coronary artery disease) and 5 had no other identifiable cardiovascular diseases. Seven patients who underwent cardiac catheterization had no detectable shunts on oximetry, and in none was a shunt demonstrated by echo contrast. In accordance with Gondi and Nanda,[16] we selected the presence of localized outpouching of the atrial septum as a qualitative definition of ASA; overall bulging of the atrial septum was excluded from our study.[22,30] Until the present study only 1 echographic study has mentioned a quantitative criterion for the amount of bulging necessary to define ASA[29]; we use 0.8 cm as the minimal amount of bulging necessary to define ASA. Our definition was based on the maximal radius of the smallest aneurysm diagnosed by subcostal 2-dimensional echocardiography and confirmed by angiography. The echocardiographic studies were performed using a commercially available sector scanner (Smith Kline Instruments, model 5,000). Patients were examined in both the supine and 30° lateral position (right and left) during quiet respiration, and the heart was visualized using parasternal, apical, subcostal transducer locations. The M-mode echograms of the ASA were recorded both from the right parasternal[31,32] and subcostal views by passing the ultrasound beam through the midportion of the ASA during each cardiac cycle. During our examinations, using the right parasternal view, M-mode recordings of the atrial septum did not always give good quality pictures; conversely, good echograms for motion analysis of the atrial septum were obtained in all cases from the subcostal view. Normal M-mode motion patterns of the atrial septum in published reports have been carried out through the right parasternal view.[31,32] We therefore studied the M-mode subcostal pattern of the atrial septum in normal subjects (Fig. 1). This pattern showed no substantial differences from M-mode curves obtained through the right parasternal approach.[31,32] Contrast echographic studies were performed using Meltzer's method,[33] both to exclude the possibility of a coexisting interatrial shunt and to give a complete morphologic evaluation of the atrial septum. The phonocardiograms and pulse tracings were recorded on a 6-channel ink-jet direct writing recorder (Elema Mingograph 81), with a piezoelectric microphone (EMT 23b), an amplifier (EMT 21)

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TABLE I Clinical Data in 23 Patients with Atrial Septal Aneurysm

Pt	Age (yr) & Sex	Clinical Findings	Cardiovascular Diseases	ECG	Echocardiographic Pattern—Motion Type (1-2-3)	Polygraphic Findings
1	79F	SVA	DCM	Normal	3	S_3
2	76F	AMI	CAD	ASI	1	Normal
3	76F	Chest pain	MVP	Normal	1	NEC
4	77M	Bradycardia	0	AVB	2	Normal
5	77M	Chest pain	CAD	LAFB	1	Normal
6	74F	SVA	SH	LVH	1	ESC
7	72F	SVA	MVP	Normal	2	NEC
8	72M	Chest pain	MVP + CAD	Normal	1	NEC
9	72F	SVA	MVP + SH	Normal	1	NEC + LSM
10	69M	SVA	MVP + SH	LBBB	3	NEC + LSM
11	68F	SVA	0	Normal	3	Normal
12	65F	SVA	MVP	LVH	2	NEC + LSM
13	63F	CHF	CAD	LBBB	3	S_3–S_4
14	63M	0	0	Normal	1	Normal
15	60M	0	DCM	Normal	3	S_3
16	60F	SVA	MVP	Normal	1	NEC + ESC
17	59F	SVA	MVP	Normal	1	NEC
18	56F	SVA	MVP	Normal	2	NEC + LSM
19	58M	Chest pain	MVP + CAD	Normal	2	NEC
20	73M	SVA	SH	LVH	3	Normal
21	51M	SVA	0	Normal	1	Normal
22	46F	SVA	0	Normal	2	Normal
23	19F	0	MVP	Normal	3	NEC

AMI = acute myocardial infarction; ASI = anteroseptal infarction; AVB = atrioventricular block; CAD = coronary artery disease; DCM = dilated cardiomyopathy; ESC = early systolic click; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LSM = late systolic murmur; LVH = left ventricular hypertrophy; MVP = mitral valve prolapse; NEC = nonejection click; S_3 = third heart sound; S_4 = fourth heart sound; SH = systemic hypertension; SVA = superaventricular arrhythmia; 0 = none.

with different filters (25, 50, 100, 200 and 400 Hz), and an arterial transducer (EMT 439a); the registrations were recorded with the patients in the supine and left recumbent positions, from the 4 standard auscultatory areas, during mild expiratory apnea and during different tests (inspiration, standing, amyl nitrite and Valsalva maneuver).

Results

Echocardiography revealed 3 motion patterns.

Type 1: In 10 patients, the ASA projected into the right atrium during diastole, with early systolic bulging into the left atrium, followed by rightward crossing-over motion in midsystole. This motion pattern appeared both during inspiration and expiration (Fig. 2, top and 3A).

Type 2: In 6 patients, ASA presented a sustained right deviation during expiration; a leftward motion occurred only during inspiration in early ventricular systole (Fig. 2, middle and 3B).

Type 3: In 7 patients, ASA remained in the right atrium, with an undulating motion during all the phases of cardiac and respiratory cycles. This type of M-mode recording results because the aneurysm is motionless except for imperceptible ripples of the wall (Fig. 2, bottom, 3C and 4).

Phonomechanocardiography showed: (1) A nonejection click in 11 patients, all with mitral valve prolapse (MVP). Four patients also had late systolic murmur. The effect of physiologic postural and pharmacologic intervention on the click and murmur yielded reproducible results in a given patient. During inspiration, standing and inhalation of amyl nitrite, the systolic click and onset of the murmur tended to move toward the first heart sound. During the overshoot

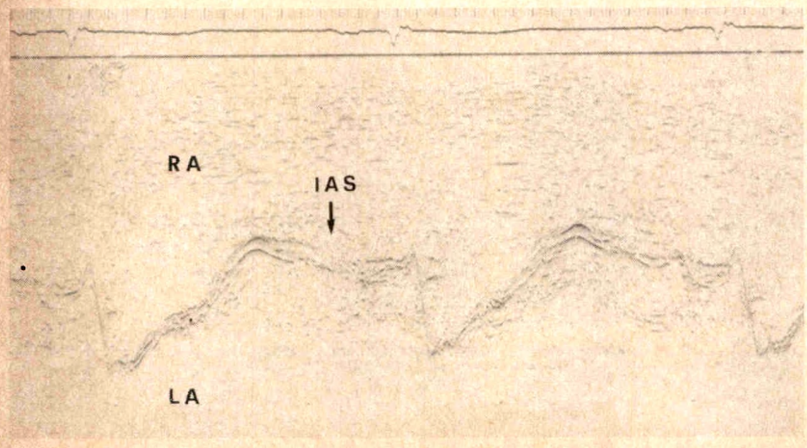

FIGURE 1. Normal M-mode pattern of the atrial septum (subcostal view). The atrial septum projects into the left atrium during early ventricular systole, and it returns toward the right atrium in midsystole. IAS = interatrial septum; LA = left atrium; RA = right atrium.

phase of the Valsalva maneuver the click and onset of the murmur were delayed. (2) Early systolic click, synchronous with the beginning of the carotid pulse upstroke in 2 patients (1 with MVP and 1 with systemic hypertension). (3) Third (S_3) and/or fourth (S_4) heart sounds in 3 patients (1 with heart failure and 2 with idiopathic dilated cardiomyopathy). (4) Carotid and jugular pulses that were unremarkable except in 1 patient (no. 3) whose ratio between preejection period and left ventricular ejection time was slightly increased.

Discussion

ASA has been reported in patients with associated congenital or acquired valvular cardiopathies, and is usually accompanied by an increased intraatrial pressure,[4–6,11–13,16,17,21,23,24] and in those without heart defects by normal intraatrial pressure.[1–3,7,8,10,14,15,18,20,22,25–29] Echocardiography makes it possible to detect this anomaly much more frequently during life (even in patients without other cardiopathies) than in the past, when diagnosis was possible

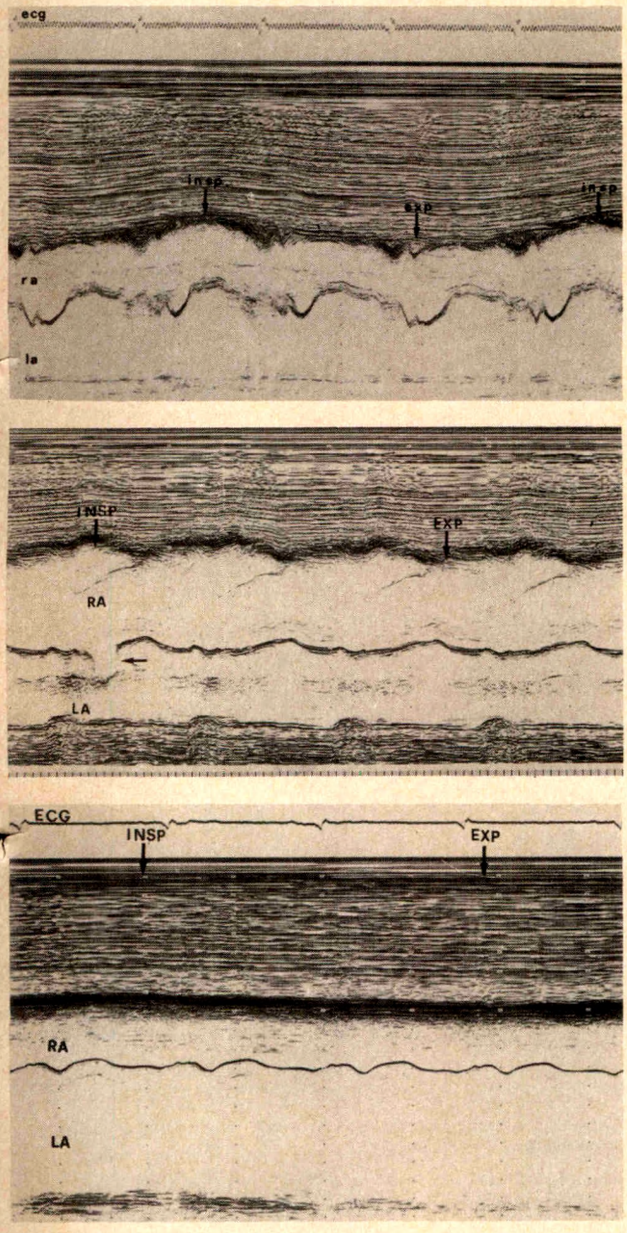

FIGURE 2. M-mode echograms of atrial septum aneurysms obtained on a cursor passing through the midportion of the aneurysms simultaneously with display of real-time cross-sectional imaging (subcostal view). **Top,** type 1 echocardiographic motion pattern; **middle,** type 2 echocardiographic motion pattern; **bottom,** type 3 echocardiographic motion pattern. ECG = electrocardiogram; EXP = expiration; INSP = inspiration; LA = left atrium; RA = right atrium.

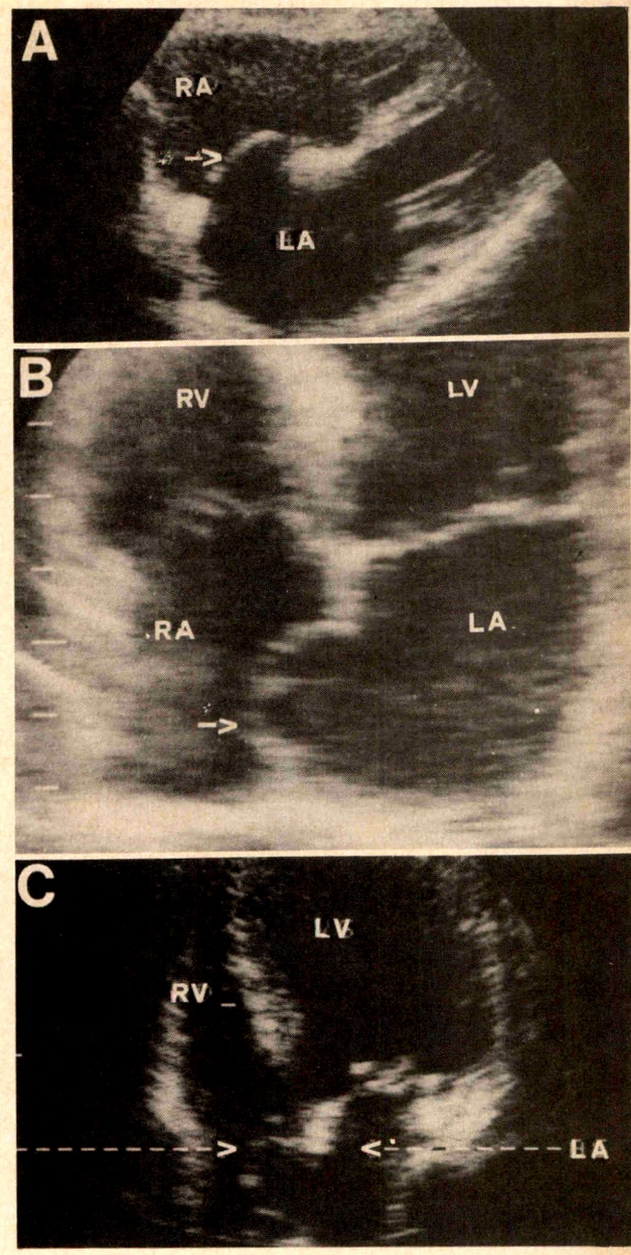

FIGURE 3. A, 2-dimensional echocardiogram of the same patient as in Figure 2, top (subcostal view). **B,** 2-dimensional echocardiogram of the same patient as in Fig. 2, middle (apical 4-chamber view). **C,** 2-dimensional echocardiogram of the same patient as in Fig. 2, bottom (apical 4-chamber view). **Arrows,** atrial aneurysms. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

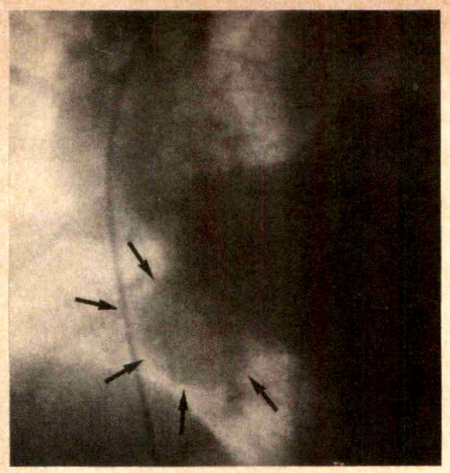

FIGURE 4. Left atrial angiogram of the same patient as in Figure 2, bottom and 3C. **Arrows,** atrial aneurysm.

only using angiographic studies.[10] Because these patients may be at risk (pulmonary or systemic emboli, obstruction of either tricuspid or mitral valve, pulmonary venous obstruction),[10,12,15,17,29] the diagnosis of ASA is important. We believed it important to verify in our patients the presence of any phonomechanocardiographic findings related to ASA, as previously, signaled in 1 case of Don Alexander et al.[18] From our study the following conclusive points emerge: (1) No phonomechanocardiographic findings were related to the presence of ASA; in particular the nonejection systolic click was found only in patients with MVP and the response of the click to various maneuvers was typical of MVP.[18,20,34,35] The other phonocardiographic findings (ejection click, S_3 and S_4) were explained by the associated cardiovascular pathology. (2) Echocardiographic findings revealed polymorphic motion patterns of ASA (the same conclusion can be reached by careful analysis of single reported cases).[18,20,24] No specific factors responsible for these different echographic patterns, such as cavity dilation or increased intracavitary pressure, were identified. We maintain that 2-dimensional echocardiography permits both a clear identification of ASA and a good evaluation of its motion patterns; in contrast, M-mode curves show neither constant nor specific patterns of ASA. (3) No correlations were found between the different echographic patterns and phonocardiographic findings in single cases.

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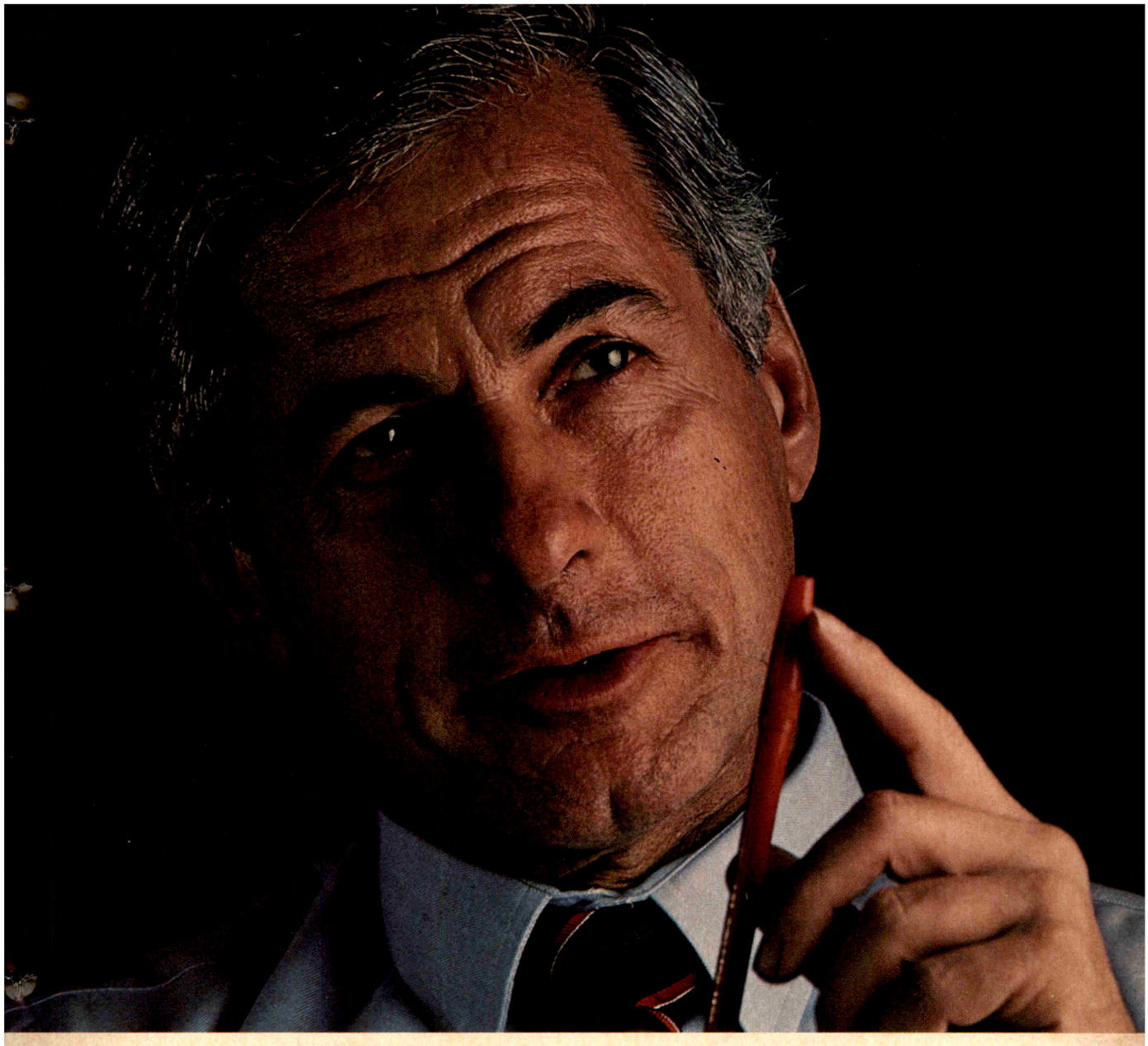

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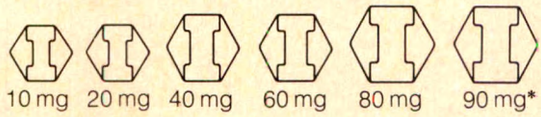

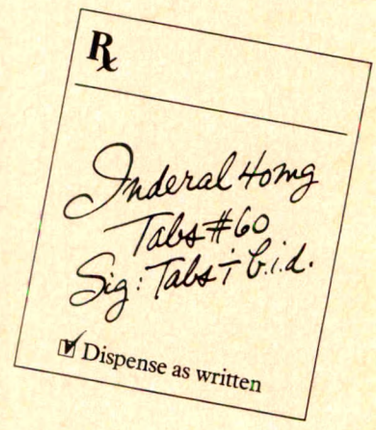

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Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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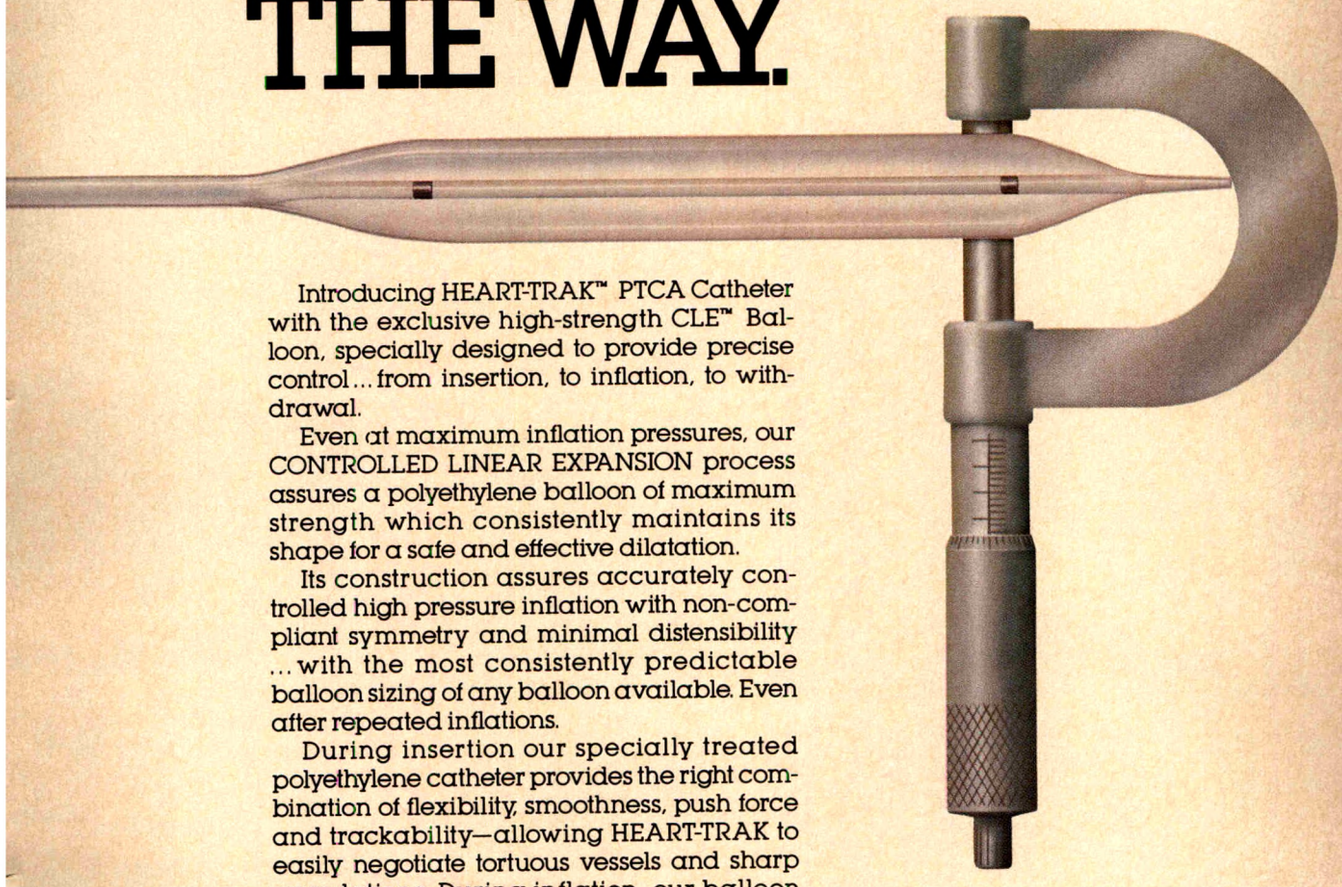

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BRIEF SUMMARY

INDICATIONS—Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency of, or eliminate, anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack. Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.
PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.
ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.
DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25, 50 and 75 mg. For complete details, please see the full prescribing information.

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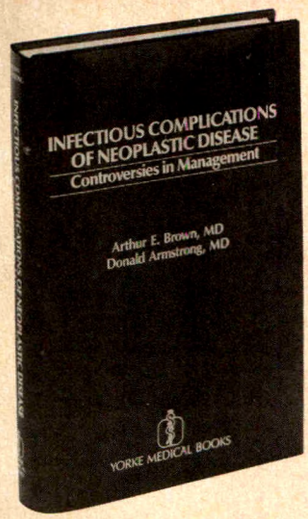

INFECTIOUS COMPLICATIONS OF NEOPLASTIC DISEASE

Controversies in Management

Edited by Arthur E. Brown, MD, and Donald Armstrong, MD
0-914316-43-5, approx. 400 pp., Oct. 1984, $40.00 casebound

About the book

Derived from a symposium sponsored by the Infectious Disease Service, Department of Medicine and the Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York City, and Cornell University Medical College, New York City, this book presents the latest thinking by international authorities, all of whom were invited to present findings in their area of expertise on the diagnosis, treatment, and prevention of various bacterial, fungal, viral, and parasitic infections presenting in patients with neoplastic disease.

This is not just another "proceedings" volume. Rather it is an edited work, with papers by investigators who submitted definitive preparations for publication. Furthermore, the authors take a strong position on their topics, ask probing questions and promote a stimulating forum of controversy.

The result is a concise, dynamic study that belongs in the professional library of every physician treating patients with neoplastic disease.

About the Editors

Arthur E. Brown, MD, is Assistant Attending Physician, Memorial Sloan-Kettering Cancer Center, and Assistant Professor of Medicine and Pediatrics, Cornell University Medical College.

Donald Armstrong, MD, is Attending Physician; Chief of Service; Director, Microbiology Laboratory, Memorial Sloan-Kettering Cancer Center, and Professor of Medicine, Cornell University Medical College

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Clinical Clues to MIXED ANGINA *No. 5*

The stairs seem steeper today

Most days she can climb the stairs with no difficulty. But today she was less than half-way up when an angina attack stopped her.

That's the unpredictability of MIXED ANGINA—vasoconstriction coexisting with fixed coronary lesion, to produce a critical reduction of myocardial blood flow.

And because vasoconstriction is an unpredictable event, ischemia and pain occur unpredictably:

- at varying levels of exercise
- at rest, or even during sleep
- upon exposure to cold
- under emotional stress
- diurnally, typically in the morning

PROCARDIA® (nifedipine) is a primary therapy for the patient with MIXED ANGINA. It prevents vasoconstriction in both large coronary arteries and coronary arterioles to maintain myocardial blood flow and oxygen supply. At the same time, PROCARDIA dilates peripheral arteries to reduce afterload and myocardial oxygen demand.

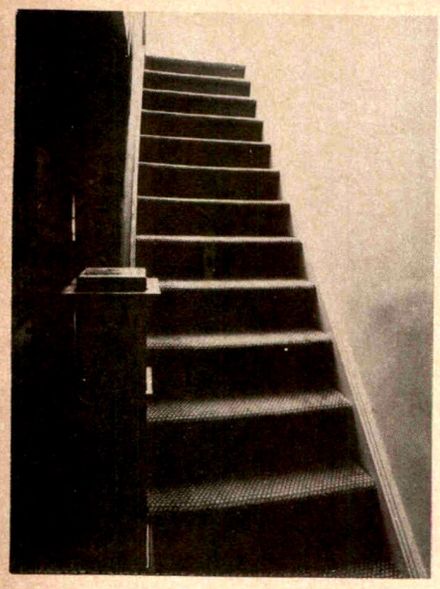
As a result, PROCARDIA can significantly reduce your patient's angina attack rate and need for nitroglycerin.[1]

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Primary Protection in
MIXED ANGINA

Please see PROCARDIA® (nifedipine) brief summary on next page.

The stairs seem steeper today



PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PRIMARY PROTECTION IN MIXED ANGINA

Usual Effective Dosage: 30 to 60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases.

A Favorable Safety Profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

Reference:

1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 106:644-652, 1983.

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA (nifedipine) therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA patients. No clinical significance for these findings has been demonstrated.

Although PROCARDIA has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to PROCARDIA therapy is uncertain in most cases but probable in some.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, mice and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cramps, flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, gingival hyperplasia, and erythromelalgia. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: Each orange soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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LABORATORIES DIVISION
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Measurement of Cardiac Output by Cine Computed Tomography

JEFFREY S. GARRETT, MD, PETER LANZER, MD, WERNER JASCHKE, MD, ELIAS BOTVINICK, MD, RICHARD SIEVERS, BS, CHARLES B. HIGGINS, MD, and MARTIN J. LIPTON, MD

High-speed computed transmission tomography (cine CT) is a new noninvasive technique that may be useful for the rapid, accurate quantitation of cardiac function. The capability of cine CT to assess cardiac output was examined 10 mongrel dogs as an initial step in validating this method. After the dogs were anesthetized, femoral arterial pressure and pulmonary artery thermodilution catheters were inserted. After intravenous injection of a bolus of contrast medium, cine CT scans were performed in the flow mode, in which 50-ms scans were triggered electrocardiographically at end-diastole at 8 levels during sequential cardiac cycles. Scans and thermodilution measurements of cardiac output were obtained at rest and during altered hemodynamic states induced by separate infusions of dobutamine and phenylephrine. Time-density analysis was performed over the left ventricular cavity and curves were fitted to the CT flow data by gamma-variate analysis. Using the Stewart-Hamilton equation established for indicator dilution techniques, the cardiac output was calculated. The results established a direct linear correlation (r = 0.92) between cine CT cardiac output and thermodilution cardiac output over a wide range of cardiac outputs (1.5 to 6.3 liters/min). This study demonstrates that cine CT can provide a reliable estimate of cardiac output noninvasively using contrast medium as an indicator in dogs.

(Am J Cardiol 1985;56:657–661)

Measurement of cardiac output is the most accurate way of assessing overall cardiovascular performance. Until recently, rapid, accurate measurement of cardiac output has not been possible using noninvasive techniques. The present investigation was designed to assess the ability of an ultra-fast, new-generation, computed axial tomographic (cine CT) scanner to measure cardiac output in dogs over a wide range of values using an indicator dilution technique.

From the Departments of Radiology and Medicine (Cardiovascular Division) and Cardiovascular Research Institute, University of California, San Francisco, California. This work was supported in part by Research Grant 1 R01 33424-01 from the National Institutes of Health, Bethesda, Maryland, and grants from the Fannie Ripple Foundation, Madison, New Jersey, the Radiology Research and Education Foundation, San Francisco, California, and Imatron, Inc., South San Francisco, California. Dr. Garrett is a recipient of Individual Research Fellowship HL-06944 from the National Institutes of Health. Dr. Botvinick is a recipient of an Established Investigator Award of the American Heart Association, Dallas, Texas, with funds contributed by local Heart Associations, and is supported in part by the George D. Smith Fund, San Francisco, California. Manuscript received February 13, 1985; revised manuscript received April 26, 1985, accepted April 30, 1985.

Address for reprints: Martin J. Lipton, MD, University of California, San Francisco School of Medicine, C-309, San Francisco, California 94143.

Indicator dilution techniques have been used since 1897 to evaluate blood flow. Stewart[1] introduced the basic theory, which was further developed by Hamilton et al[2] and applied to the measurement of cardiac output.[3] Thermodilution and hydrogen indicator dilution techniques are widely used and have emerged as practical and reproducible. Contrast medium is an alternative indicator that may be used to assess cardiac output provided that continuous sampling of the indicator is possible to determine density (concentration) vs time. This study was performed to determine whether the rapid, repeated densitometric measurements obtained with the use of a noninvasive CT technique can permit the accurate assessment of cardiac output while simultaneously providing structural cardiac detail.

Methods

Ten mongrel dogs (28 to 32 kg) were anesthetized with sodium pentobarbitol (25 mg/kg) and Innovar® (10 mg/kg) and intubated. Respiration was maintained and controlled at 16 breaths/min with a Harvard pump respirator. Continuous pressure monitoring was performed with a catheter inserted into the femoral artery. A Swan-Ganz thermodilution catheter

was inserted through the femoral vein and advanced into the pulmonary artery and a separate venous catheter was inserted and advanced to the midportion of the inferior vena cava. Electrocardiograms were continuously monitored and recorded during scanning. Cardiac output was measured by thermodilution using an Edwards cardiac output computer and from measurements made during simultaneous CT scanning. Measurements were performed in the control state, before pharmacologic intervention, and after sequential 20-minute infusions of dobutamine (10 μg/kg/min) and phenylephrine (0.025/mg/kg/min).

CT scanning was performed on the first production fast (cine) CT scanner[4] (Imatron, Inc.). The cine CT scanner design incorporates an electron beam, which replaces the heavy,

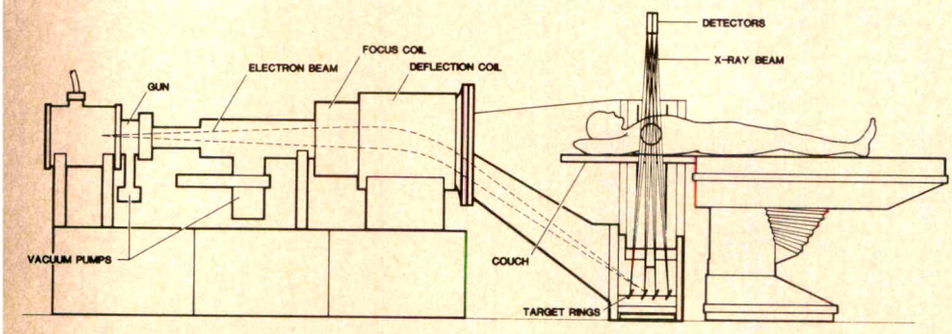

FIGURE 1. Imatron C-100 scanner. An x-ray fan is produced when an electron beam, focused by a magnetic field is swept along tungsten target rings.

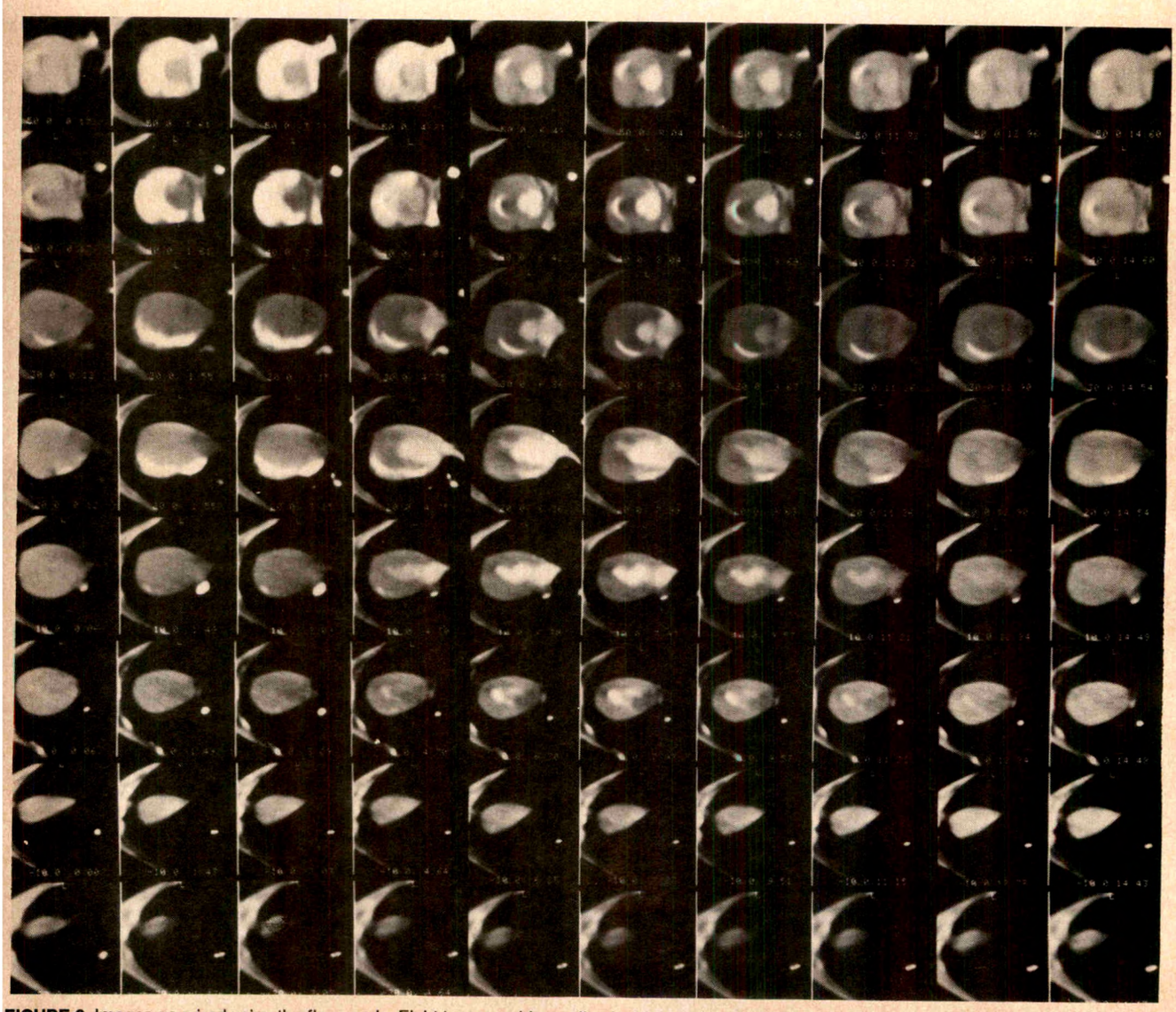

FIGURE 2. Images acquired using the flow mode. Eight tomographic cardiac levels are displayed. The bolus is observed passing sequentially from the right to left side of the heart. The entire series of images displayed was obtained in under 20 seconds.

rotating x-ray tube present in whole-body CT scanners. The electron beam is bent and focused by a magnetic field and acquires as many as eight 1-cm-thick tomographic levels simultaneously (Fig. 1). The scan exposure time is 50 ms. All images were acquired in this study during full inspiration with the dog in the right lateral position on the scanning table. Scan acquisition was electrocardiographically triggered at 80% of the averaged length of the proceeding 7 RR intervals, so that all scans for successive cardiac cycles were acquired in diastole.

Scans were acquired for approximately 20 seconds after the intravenous administration of a 10-ml bolus of iothalamate sodium (Conray 400) (Fig. 2). Time-density analysis was performed over a left ventricular region of interest and curves were fitted to the CT flow data by a least-squares gamma-variate analysis,[5] thus correcting for recirculation. This was done at 3 ventricular levels and the areas under these curves were obtained. Thermodilution measurements were performed in triplicate. Intracavitary regions of interest were manually defined over the ventricle. The hypothesis that the areas obtained by the time-density analysis at each of the 3 ventricular levels were the same, was tested by repeated measures analysis of variance using the following regression model:

$$\text{Area} = A + B(L1) + C(L2) \quad (1)$$

where AREA = area obtained by the time-density analysis, A, B, C = regression coefficient and L1 and L2 = dummy independent variables representing the 3 ventricular levels. L1 was defined at 1 for level 1, 0 for level 2 and −1 for level 3 and L2 was defined as 0 for level 1, 1 for level 2, and −1 for level 3.[6] F was calculated as

$$\frac{\text{Mean sum of squares regression}}{\text{mean sum of squares residual}} \quad (2)$$

and was evaluated at the 0.05 level.

Cardiac output was calculated using the standard Stewart-Hamilton[3] equation:

$$CO = X/c(t)dt \quad (3)$$

where CO = cardiac output, X = quantity of indicator injected into the system and c(t) = concentration at the sampling site at time t. This concentration value may be modified to account for the measurement of the contrast density instead of absolute concentration, provided that there is a linear relation between indicator (iodine) concentration and CT number over the range of the study. Equation 3 therefore becomes

$$CO = (X)(A)/D(t)dt \quad (4)$$

where D(t) = density in CT numbers at the sampling site at time t and A = constant of proportionality relating c(t) to D(t). If a constant sized bolus of indicator is used, the equation then becomes

$$CO = K/D(t)dt. \quad (5)$$

Equation 5 may therefore be applied to the measurement of cardiac ouput, provided the following conditions are met: (1) The contrast indicator must have the same distribution of transit times as that of the blood. (2) Recirculation phase of the indicator is excluded prior to computing the cardiac output. (3) All of the contrast medium eventually leaves the heart. (4) Cardiac output is not changing while the measurement is being made. (5) Negligible contrast medium is lost during transit through the lungs.[7]

The densitometric system used to measure indicator concentration was validated in phantom experiments. A water phantom measuring 31 cm in diameter was constructed of Plexiglas®. The phantom contained a peripherally placed hollow core (4.5 cm diameter) (Fig. 3). The core was filled with a range of concentrations of standard iothalamate sodium contrast medium (0 to 38 mg iodine/ml) to approximate the concentration of the diluted bolus at the cardiac level. These phantoms were scanned and cine CT densitometric measurements were performed.

Results

The accuracy of indicator dilution techniques relies on the ability to precisely measure indicator concentration. Phantom measurements demonstrated linearity of CT number vs indicator concentration over the density range considered in this study with a correlation coefficient of 0.99 (Fig. 4).

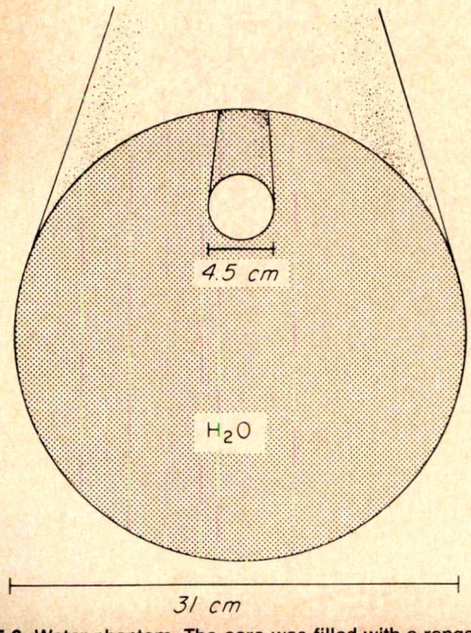

FIGURE 3. Water phantom. The core was filled with a range of concentrations of contrast medium and the phantom was scanned to verify the relationship between CT density and absolute concentration.

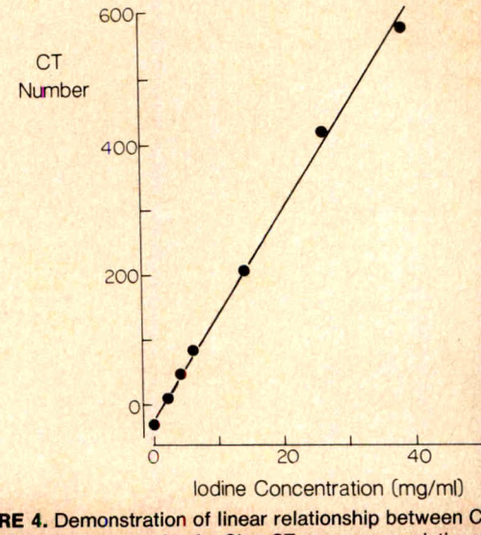

FIGURE 4. Demonstration of linear relationship between CT number and indicator concentration for Cine-CT scanner correlation coefficient (R)-0.99.

Figure 5 represents a typical time-density analysis used to quantitate cardiac output in a dog. Once a region of interest over the ventricular cavity was selected, the mean CT number for that region was automatically plotted for each sequential scan vs lapsed time from onset of injection. The cine CT scanner performed this analysis on line within 1 to 2 seconds. The gamma-variate fit was then superimposed on the individual measurements, and the area under the curve was calculated and displayed on the cathode ray viewing screen.

The regression model (equations 1 and 2) was applied to test for the interlevel variability of the area. F was equal to 0.16 ($p < 0.05$) thus, demonstrating that no significant interlevel variability was present.

K (equation 5) was calculated from the slope of the CT density-iodine concentration relation (Fig. 4). There was high correlation ($r = 0.92$) for cine CT–determined cardiac output and thermodilution cardiac output over a wide range of cardiac outputs (1.5 to 6.3 liters/min) (Fig. 6).

Discussion

Many techniques are available to assess cardiac output, including thermodilution, oxygen consumption, nuclear and Doppler methods.[8] Conventional CT scanners may be used to assess cardiac output[9]; however, they have a limited role in cardiac diagnosis. The major problems of conventional CT scanners is the relatively long exposure time of 1 to 5 seconds compared with the length of the cardiac cycle. This is compounded by the long interscan delay time and single slice configuration.

The cine CT scanner uses a revolutionary solution to these problems and makes possible the simultaneous evaluation of structure and function. Cine CT scanning is a digital tomographic technique that minimizes the problem of misinterpretation due to overlying structures inherent in traditional cardiac radiographic techniques and provides outstanding spatial resolution at multiple cardiac levels. We have demonstrated that it is possible to acquire noninvasively an indicator (density) curve over time using a cine CT scanner and a small amount of peripherally administered contrast medium. This information may then be used to accurately assess the cardiac output. Because this curve is, in fact, generated from densitometry of discrete images, anatomic measurements at multiple tomographic levels may be made from images obtained with a single bolus injection.

The time-density analysis technique for the measurement of cardiac output assumes that the selected region of interest from which the time-density data is compiled is always either intravascular or intracavitary, and the number of pixels included in the region of interest are maximized so that sampling error is minimized. If the selected region of interest is not reproducibly intravascular or intracavitary (i.e., the vessel or cavity has moved away from the selected region), then an error occurs, which is termed "partial volume effect." The partial volume effect results from the sampling of pixels on serial images that are geometrically but not anatomically identical. We have found that intracavitary regions of interest minimizes partial volume effects while maximizing the number of pixels sampled. Left ventricular regions of interest are especially suited to cardiac output determinations because this is the site of the most complete mixing of the contrast agent with the blood pool.

Contrast medium has hemodynamic effects which may alter the determination of of cardiac output by cine CT.[10] It may be possible to eliminate this potential source of error by using nonionic contrast agents. Possible hemodynamic effects of contrast media on the determination of cardiac output were not severe enough

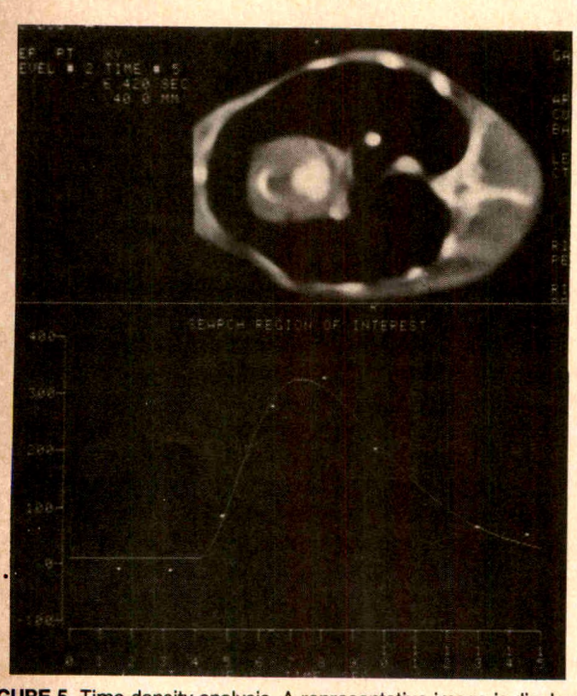

FIGURE 5. Time-density analysis. A representative image is displayed with a region of interest defined over the left ventricle (above). CT density is plotted vs time (below) and the gamma variate fit is superimposed.

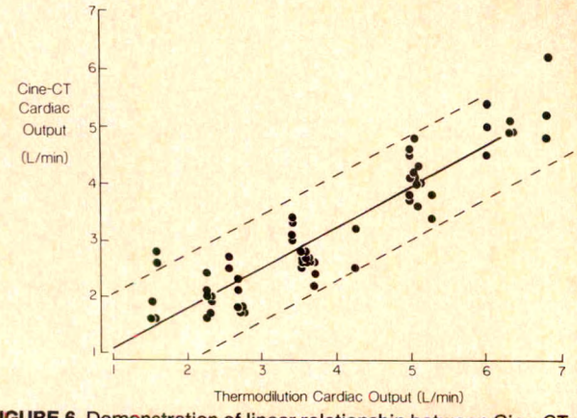

FIGURE 6. Demonstration of linear relationship between Cine-CT and thermodilution cardiac outputs. East squares regression line is solid; confidence intervals (95%) are **broken lines. Solid circles** are the individual data prints. Correlation coefficient (r) = 0.92.

in the current study to vitiate the close correlation between CT and thermodilution measurements.

If images are acquired at the maximum rate of 17 scans/s (50 ms/scan), regional myocardial wall thickening can also be evaluated because CT displays both the endocardial and epicardial walls.[11] The indicator dilution technique for cine CT described in this report applied in conjunction with the advanced graphics capabilities of the scanner's computer can also provide documentation and quantification of intracardiac shunts. The precision of such measurements remains to be determined and validated. Cine CT is a new technique for cardiologic diagnosis with a unique potential for qualitative and quantitative analysis of anatomic variables of ventricular function while noninvasively evaluating physiologic variables during the same procedure.

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Reduction of Laser-Induced Pathologic Tissue Injury Using Pulsed Energy Delivery

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Continuous-wave (CW) laser irradiation of cardiovascular tissues is characterized by 2 distinctive histologic findings: a superficial zone of coagulation necrosis and a subjacent zone of polymorphous lacunae. The present investigation was designed to determine whether such injury could be eliminated by altering the temporal profile of laser energy delivery. One hundred forty-five myocardial slices were irradiated with an air-tissue interface using CW laser irradiation at wavelengths of 488 to 515 nm (argon), 1,064 nm (Nd-YAG) and 10,600 nm (CO_2). Pulsed laser irradiation included 248 nm (excimer); 355, 532 and 1,064 nm (Nd-YAG); and 515 nm (mode-locked argon). Energy profiles in the pulsed mode included a range of repetition rates (1 Hz to 256 MHz), pulse duration (0.2 to 358 ns) and pulse energies (2 nJ to 370 mJ). Resultant average powers were 0.1 to 38 W. Grossly visible charring of myocardial tissue was observed at all laser wavelengths when the laser energy profile was CW or pulsed at high repetition rates (more than 2 KHz) and low pulse energies (less than 3 mJ) independent of the wavelengths used. In contrast, when laser energy was pulsed at low repetition rates (less than 200 Hz) and large pulse energies (more than 10 mJ), neither gross nor histologic signs of thermal injury were observed.

Pathologic injury associated with laser-induced tissue ablation may thus be substantially reduced by use of pulsed energy delivery at low repetition rates. Potential advantages of pulsed laser energy include a more benign healing process, a less thrombogenic surface, and improved preservation of structural tissue integrity.

(Am J Cardiol 1985;56:662–667)

Previous investigations[1–9] have established the potential utility of laser irradiation in the treatment of cardiovascular disorders. Previous studies have also shown that continuous-wave (CW) laser irradiation of cardiovascular tissues is characterized by 2 distinctive histologic findings: a superficial zone of coagulation necrosis and a subjacent zone of polymorphous lacunae. The former has been attributed to thermal injury,[3,10–12] whereas the latter has been interpreted to result from "acoustic" or "shock" injury.[12,13]

Laser energy can be delivered in a time-varying fashion that is characterized by the laser energy profile, a profile of power output over time. CW lasers have a power output that is constant over time. In contrast, pulsed lasers deliver energy in brief, discrete pulses, each of which is separated by an emission-free interval. There are at least 2 reasons why laser irradiation delivered in the pulsed mode may be expected to cause less damage to tissues adjacent to the target site: If the period of absent energy transmission between pulses is long enough, heat generated during the pulsed emissions might be expeditiously dissipated, preventing thermal tissue damage; alternatively, the higher peak powers characteristic of pulsed lasers may result in a large photon density sufficient to ablate tissue by a nonthermal mechanism.

Accordingly, the present study was designed to determine whether the extent of pathologic injury resulting from laser irradiation of cardiovascular tissue could be reduced by alterations in laser energy profile.

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Methods

Tissue: Slices of myocardium obtained in the fresh state from human cadavers or laboratory dogs were used for all experiments. Myocardium was selected on the basis that a standardized preparation—in this case homogeneous tissue with a uniform slice thickness of 0.5 cm—was required to provide a meaningful comparison among various laser wavelengths and energy profiles. Furthermore, studies both in our laboratory[7,8,14] and in other laboratories[3,15] have consistently shown that histologic alterations resulting from laser irradiation are not tissue-dependent; i.e., for a given wavelength and energy profile, laser irradiation of myocardium, atherosclerotic coronary arteries, and calcified aortic valve leaflets produces similar histopathologic changes in all 3 tissues.

Lasers: *CW lasers* used in this study included an argon laser (Coherent, Inc.) a carbon dioxide (CO_2) laser (Cavitron,

TABLE I Energy Profile and Tissue Injury: Continuous Laser Irradiation

Laser	λ (nm)	Power (W)	Exposure (sec)	Energy (J) (mean ± SEM)	No. of Spec.	TC
Argon*	488–515	1–3	42–100	98 ± 6	10	+
Nd-YAG*	1064	4–38	6–62	205 ± 26	11	+
CO_2†	10,600	5–24	3–24	110 ± 12	7	+

* Fiber.
† Focused beam.
Nd-YAG = neodymium-yttrium-aluminum-garnet; SEM = standard error of the mean; Spec. = specimens; TC = tissue charring; + = present; λ = wavelength.

Inc.), and a neodymium:yttrium, aluminum, garnet (Nd-YAG) laser (Biolase, Inc.). *Pulsed lasers* included an argon laser (Spectra Physics), 2 krypton fluoride excimer lasers (Lambda Physik, Questek, Inc.) and 2 Ng-YAG lasers (Quantel International, Quantronix Corp). The argon lasers and the CW Nd-YAG laser were coupled to a flexible silica fiber, 200 to 600 μ in diameter. The fiber was positioned approximately 0.5 mm above the myocardial tissue to yield an incident spot size of 0.5 to 1 mm^2. The CW CO_2 laser and the pulsed lasers other than argon emitted an energy beam that was directly incident on the myocardial slice or that was focused through a lens onto the tissue. Incident spot size of the unfocused beam was 0.8 mm^2. Incident spot size of the focused beam was approximately 0.2 mm^2.

All myocardial specimens were irradiated with an air-tissue interface on an optical stage. The endpoint for laser irradiation was the time required to bore through the 0.5-cm-thick specimen and was detected using either a light meter or photosensitive paper placed underneath the tissue.

Average power delivery (in watts) was verified with an external laser power meter (Coherent, Inc.). Repetition rate, i.e., the number of pulses per second in hertz, and pulse duration were predetermined. Pulse amplitude (in joules) was calculated as average power divided by repetition rate. Peak power (in watts) was calculated as pulse amplitude divided by pulse duration.

Analysis of tissue injury: Each specimen was examined in the fresh state, immediately after completion of laser irradiation, for gross evidence of tissue charring, defined as gross blackening or apparent carbonization at the perimeter of the tissue crater; the gross appearance of selected specimens was documented by macrophotography. The specimen was then cut into divided halves, parallel or perpendicular to the laser-irradiated surface, processed routinely for light microscopic examination, and stained with hematoxylin-eosin and Gomori's trichrome stain.

The remaining half of the specimen was prepared for scanning electron microscopy with principal fixation in 0.1 *M* cacodylate-buffered 3% glutaraldehyde (pH 7.3), postfixed with 0.1 *M* cacodylate buffered 1% osmium tetroxide (pH 7.3), washed and dehydrated. After critical point drying, the specimen was coated with gold-palladium (40:60) and examined using an AMRAY-1,000 scanning electron microscope.

Results

A total of 145 slices of myocardium, 0.5 cm thick, were irradiated using an air-tissue interface. The lasers used, details of the energy profile, and the presence or absence of tissue charring are summarized in Tables I (CW) and II (pulsed lasers).

Continuous-wave lasers (Table I, Fig. 1): *Argon laser:* Gross tissue charring was observed in each specimen. Light microscopic examination (Fig. 1) consis-

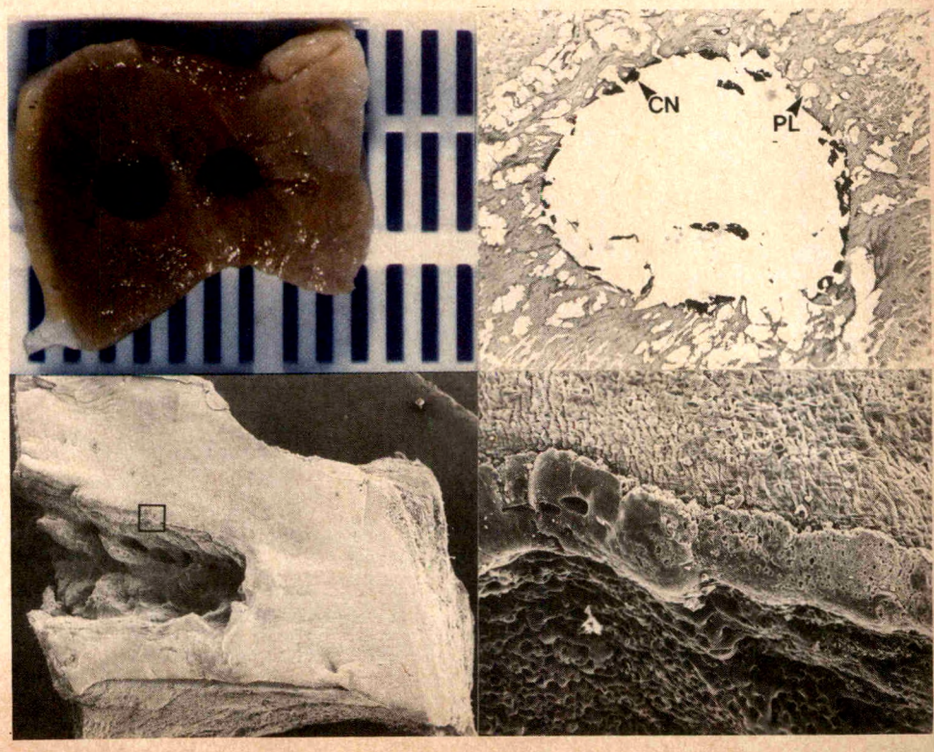

FIGURE 1. Gross, light microscopic and ultrastructural injury resulting from continuous wave (CW) laser irradiation. **Upper left,** gross photograph of 2 separate craters accomplished with 1,064 nm from a CW Nd-YAG laser, using 34 W for 7 seconds (left crater) and 4 W for 120 seconds (right crater). Charring is seen at the perimeter of each crater. **Upper right,** typical light microscopic findings following CW argon laser irradiation, using 3 W for 22 seconds. There is a superficial zone of coagulation necrosis (CN) and a subjacent zone of polymorphous lacunae (PL). **Lower left,** scanning electron photomicrograph of surface of one-half of a myocardial crater accomplished with CW argon laser, using 1.4 W for 5 seconds. Thermal injury at the perimeter of the crater is apparent; high-power view of the portion of injured perimeter indicated by **box** is shown at **lower right.** The superficial zone of coagulation necrosis measures 100 to 120 μ in width; lacunae along the wall of the crater measure 13 to 36 μ in diameter. **Upper right,** hematoxylin-eosin [H-E] × 10; **lower left** × 21.9; **lower right** × 219—reduced by 50%.

TABLE II Energy Profile and Tissue Injury: Pulsed Laser Irradiation

Laser	λ (nm)	Rep. Rate (Hz)	PA (mJ)	PD (ns)	Power (W)		Exposure (sec)	Energy (J) (mean ± SEM)	No. of Spec.	TC
					Peak	Avg				
Argon*	515	256×10^6	$2–5 \times 10^{-6}$	0.2	10–23	0.5–1.2	21–191	55 ± 7	11	+
Nd-YAG†	532	$2–10 \times 10^3$	0.1–0.5	96–190	$0.7–5 \times 10^3$	1–1.5	11–92	47 ± 7	15	+
Nd-YAG‡	532	$2–10 \times 10^3$	0.1–0.5	96–190	$0.7–5 \times 10^3$	1–1.5	2–19	10 ± 2	14	+
Nd-YAG†	1,064	$2–10 \times 10^3$	1–2.7	140–358	$3–18 \times 10^3$	2–10.5	15–83	403 ± 68	6	+
Excimer‡	248	1–200	10–370	15	$0.7–25 \times 10^6$	0.5–37	1–68	22 ± 3	19	0
Nd-YAG‡	355	2–10	60–88	20	$3–4 \times 10^6$	0.1–0.9	8–109	14 ± 4	8	0
Nd-YAG‡	532	2–10	60–190	20	$3–9 \times 10^6$	0.4–1.9	7–74	12 ± 1	31	0
Nd-YAG‡	1,064	10	190–250	20	$9–12 \times 10^6$	1.9–2.5	6–26	24 ± 3	13	0

* Fiber.
† Direct beam.
‡ Focused beam.
Avg = average; ns = nanoseconds (10^{-9} seconds); PA = pulse amplitude; PD = pulse duration; Rep. Rate = repetition rate; 0 = absent; other abbreviations as in Table I.

tently disclosed a superficial zone of coagulation necrosis and a subjacent zone of polymorphous lacunae. Scanning electron microscopy (Fig. 1) confirmed the histologic findings: a superficial coagulum covered an extensive network of lacunae, which along the walls of the trough ranged from 13 to 36 μ.

Nd-YAG: Gross tissue charring was observed in each specimen (Fig. 1). Light microscopic and ultrastructural findings were identical to those observed with CW argon and CO_2.

CO_2 laser: Gross tissue charring was observed in each specimen. Light microscopic and ultrastructural findings were identical to those observed with CW argon.

Pulsed lasers with high repetition rate (Table II) (Fig. 2): *Argon laser:* Gross, light microscopic (Fig. 2) and ultrastructural (Fig. 2) findings in each case were similar to those observed with CW argon.

Nd-YAG: Specimens were irradiated with 532 and 1,064 nm at 2 to 10 kHz. Gross, light microscopic and ultrastructural findings in each case were similar to those observed for pulsed argon.

Pulsed lasers with low repetition rate (Table II, Fig. 3): *Excimer:* Gross evidence of tissue charring was not observed in any specimen. Light microscopy in some cases disclosed no alteration of the residual laser-irradiated tissue; in other cases (Fig. 3), discontinuous linear discoloration (basophilic with hematoxylin and eosin; magentoid with trichrome stain) at the perimeter of the laser crater was observed. Scanning microscopy (Fig. 3) indicated that this light microscopic finding corresponded to "wrinkling" or "pruning" of the myocytes directly adjacent to the laser crater. Rare, sparsely distributed lacunae were seen.

Nd-YAG: Specimens were irradiated with 355, 533, and 1,064 nm at 2 to 10 Hz. Gross tissue charring was not observed in any specimen. Light microscopic and ultrastructural findings were qualitatively and quantitatively similar to those observed with the excimer laser.

In summary, grossly visible charring of myocardial tissue was observed at all laser wavelengths when the laser energy profile was continuous or pulsed at high repetition rates (higher than 2 kHz) with low pulse energies (less than 3 mJ). Charring was absent when laser irradiation was delivered in the pulsed mode at low repetition rates (less than 200 Hz) with high pulse energies (more than 10 mJ), independent of the wavelengths used. Tissue charring observed on gross examination consistently was associated with light microscopic findings of coagulation necrosis and polymorphous lacunae. In the absence of gross tissue charring, these light microscopic findings were not observed. Likewise, scanning microscopy consistently confirmed the histologic findings associated with gross charring and, in the absence of charring, disclosed only wrinkling or pruning of the myocytes bordering the laser crater. The extent of ultrastructural alteration of myocytes adjacent to the laser crater was, in the worst case, limited to less than 650 μ in each specimen irradiated with a pulsed laser at low repetition rates. Both this finding, as well as the presence or absence of the light microscopic correlate (linear discoloration), could not be correlated with a single specific variable of the pulsed energy profile.

Discussion

Pathologic examination of cardiovascular tissues irradiated with CW lasers has consistently disclosed gross charring at the perimeter of the laser crater, and distinctive light microscopic findings: a superficial, linear zone of coagulation necrosis, and a subjacent zone of polymorphous lacunae.[1–9] Furthermore, the photoproducts generated by CW laser irradiation of cardiovascular tissues have been shown to be those typical of a thermal process.[10] Thus, these gross and histologic findings have been interpreted as the result of thermal injury. The results of the present investigation suggest that gross and light microscopic signs of injury associated with CW laser tissue ablation can be eliminated by pulsed energy delivery using high peak powers and low repetition rates.

CW lasers used in an "intermittent" or "chopped" mode must be differentiated from a true pulsed laser. The CW laser may be used in 2 ways: continuous or

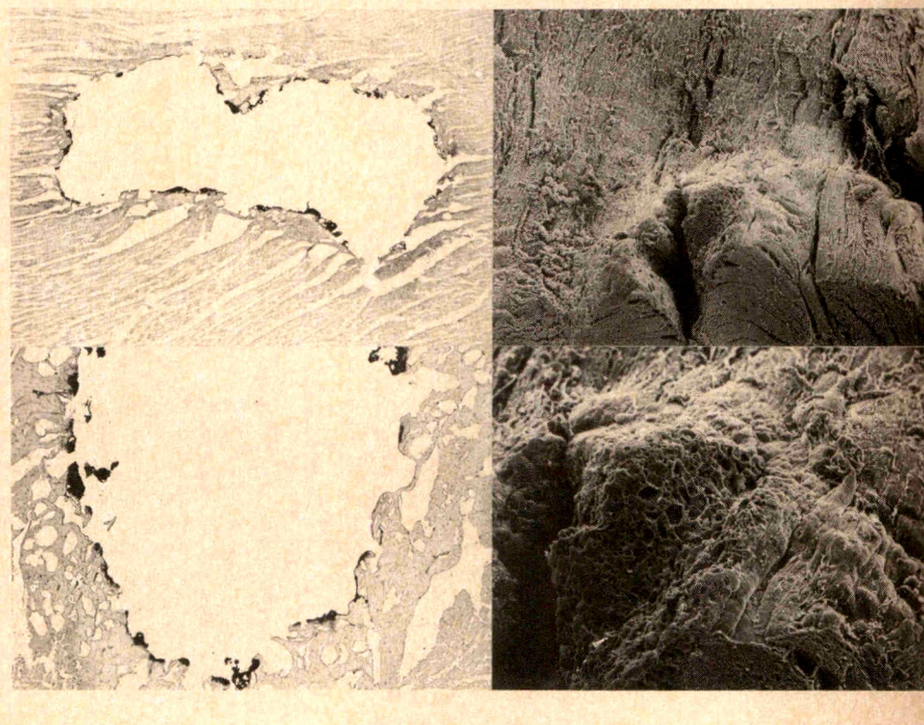

FIGURE 2. Light microscopic and ultrastructrual findings after pulsed laser irradiation with high repetition rate. **Upper** and **lower left,** light microscopic findings of coagulation necrosis and polymorphous lacunae resulted from mode-locked argon laser (515 nm, 256 MHz, 65-second exposure, average power = 0.7 W) (**upper left**) and pulsed Nd-Yag (1,064 nm, 10 KHz, 29 seconds, 10.5 W). (**Upper** and **lower right**): scanning electron photomicrographs of thermal injury resulting from mode-locked argon laser (515 nm, 256 MHz, 33 seconds, 1.0 W) **upper left,** H-E × 10; **lower left,** H-E × 25; **upper right,** × 31.6; **lower right,** × 100—reduced by 50%.

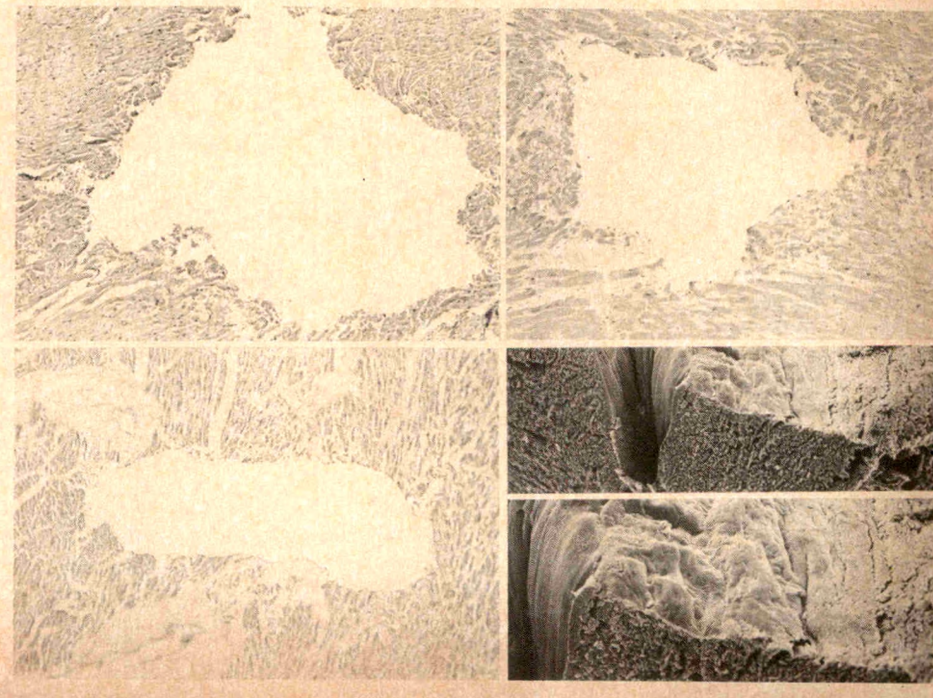

FIGURE 3. Light microscopic and ultrastructural findings after pulsed laser irradiation with low repetition rate. Neither of the typical light microscopic signs of thermal injury (coagulation necrosis and polymorphous lacunae) are observed after pulsed laser irradiation with (**upper left**) Nd-YAG-532 (10 Hz, 3-second exposure, 350 mJ); (**upper right**) Nd-YAG (1,064 nm [10 Hz, 7 seconds, 190 mJ]); and (**lower left**) excimer (248 nm [10 Hz, 5 seconds, 250 mJ]). Scanning electron photomicrograph at **lower right** shows lower power (× 62.1) and higher power (× 101) views of myocardial trough after excimer laser (200 Hz, 41 seconds, 3 mJ) irradiation. The walls of the trough are smooth with only rare lacunae. The surface at the perimeter of the trough has a wrinkled pruned appearance. **Upper left,** H-E × 25; **upper right,** H-E × 25; **lower left,** H-E × 4, reduced by 50%.

periodically interrupted. The latter has been referred to as an intermittent or chopped mode. Intermittent or chopped differs from continuous delivery only with respect to emission-free intervals; power output during intervals of laser emission is identical for both modes. This is in marked contrast to true pulsed lasers. In common with the chopped mode, pulsed lasers include emission-free intervals. Unlike chopped lasers, however, pulsed lasers use a variety of techniques (e.g., mode-locking or Q-switching) that allow energy storage within the laser cavity; as a result, each emission is characterized by a peak power substantially greater than the continuous power output of a CW laser.

The distinction between chopped and pulsed, as well as considerations regarding pulse duration and repetition rate, are directly relevant to the reduction in laser-induced tissue injury demonstrated in this study. Experiments by Hayes and Wolbarsht,[12] Welch,[16] and Anderson and Parrish[17] have suggested that thermal injury of adjacent, nontarget tissues can be avoided when exposure time used for each pulse is shorter than the thermal relaxation time (characteristic time for first-order temperature dissipation) of the irradiated tissue. If the pulse duration and cumulative exposure are sufficiently brief, and if the interval between each pulse is sufficiently long, then the heat generated by each pulse may be sufficiently dissipated before delivery of the subsequent pulse. Consequently, thermal injury of tissue outside the path of the laser beam can be avoided.

Although pulsed delivery at low repetition rates in an air-tissue interface clearly eliminates gross microscopic evidence of thermal injury, studies demonstrating that these findings can be reproduced in a blood-filled system are needed. Furthermore, the present series of experiments does not establish that this superior histologic appearance is a result of enhanced dissipation of heat during the thermal process or a nonthermal (photochemical[18] or photodisruptive[19] process. To achieve a given volume of tissue ablation, if the number of pulses and the duration of each pulse are reduced, then sufficient power (watts) can be achieved only by increasing pulse energy. As a result, pulsed lasers with low repetition rates and brief pulse durations are characterized by high peak powers (pulse energy/pulse duration). Consequently, the effects of improved thermal relaxation (accomplished at reduced repetition rate and pulse duration) are difficult to separate from those of high peak power. In the present series of experiments, for example, peak powers unassociated with pathologic tissue injury were consistently in the megawatt range. The photon density resulting from such peak powers may possibly ablate tissues by a nonthermal process.

Athough the absence of charring was observed only with energy profiles that necessitated the use of a focusing lens, this smaller spot size and resultant higher photon density alone did not account for the absence of pathologic injury. Both the CW argon laser and the rapidly pulsed (more than 2 kHz) Nd-YAG laser resulted in pathologic injury when used with a focusing lens.

The choice of myocardial slices for these experiments was based on the requirement for homogeneous tissue with uniform slice thickness that would allow meaningful comparison among various laser wavelengths and energy profiles. The optimal combination of energy profile and wavelength for atherosclerotic segments of coronary arteries may vary from those used to irradiate myocardium. Nevertheless, our experience with excimer laser irradiation[20] suggests that the reduction in pathologic injury of myocardium accomplished by pulsed energy delivery is transferrable to atherosclerotic plaque.

Elimination of pathologic alterations such as coagulation necrosis and polymorphous lacunae in residual laser-irradiated tissue is potentially advantageous. A more benign healing process, a less thrombogenic surface, and improved preservation of structural tissue integrity may be reasonably anticipated. However, these remain only potential advantages; no long-term, in vivo data are available. Furthermore, chronic (albeit relatively short-term and relatively limited) studies involving CW laser irradiation[21,22] have failed to establish clearly deleterious consequences of thermal injury associated with CW laser irradiation.

Finally, because the high peak powers characteristic of the energy profiles used here to avoid pathologic tissue injury cannot be coupled to commercially available fiberoptics, clinical application of these energy profiles must be limited to direct surface (e.g., intraoperative) irradiation. Even with this restriction, however, such energy profiles may be used to advantage, e.g., to perform intraoperative ablation of pathologically thickened endocardium.[8] The absence of any tissue charring in such a procedure would facilitate recognition of underlying myocardium after ablation of the overlying endocardial scar. Percutaneous application of these pulsed profiles, however, will require development of fiberoptics and coupling mechanisms capable of transmitting such high peak powers.

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Effects of Hematoporphyrin Derivative and Photodynamic Therapy on Atherosclerotic Rabbits

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This study was performed to demonstrate selective uptake of hematoporphyrin derivative (HPD) within actively developing atheroma, to localize the site of uptake of HPD within the atheroma, and to determine the potential for photodynamic therapy (PDT) of atherosclerosis in the rabbit model. Fifteen rabbits were rendered atherosclerotic. Five rabbits received neither HPD nor PDT and 2 rabbits received HPD, 10 mg/kg intravenously, without subsequent irradiation. Eight other rabbits received 5 to 20 mg of HPD intravenously and subsequent intravascular 636-nm laser radiation to either the thoracic aorta or the aortic arch. A total of 32 to 288 J of laser energy was delivered through a 300-μ quartz fiber. All rabbits that received in vivo HPD had red fluorescence of their aortas when placed under ultraviolet light. The pattern of fluorescence corresponded precisely to the pattern of atheroma. In segments that received PDT, light microscopic examination revealed an accumulation of smooth muscle cells at the intimal surface. Fluorescence microscopy revealed a diminishing concentration gradient of HPD from intimal surface layers towards the media. Assessment of treated thoracic aortic segments revealed quantitative and qualitative differences compared with control segments. In the arch-treated segments, however, no changes were seen. It is concluded that HPD localizes within rabbit atheroma, can be detected by fluorescence and is deposited in a diminishing concentration gradient from lumen toward media. Irradiation with 636-nm light may induce qualitative and quantitative changes in atheroma.

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Naturally occurring porphyrins accumulate in rapidly proliferating cells.[1] Hematoporphyrin derivative (HPD), made from natural hematoporphyrin,[2] has been used for the diagnosis and treatment of neoplastic disorders.[3–7] HPD possesses 2 characteristics that make it useful for these purposes. First, when irradiated with ultraviolet light, HPD fluoresces, allowing for detection of HPD containing cells.[3,4,8] Second, when irradiated with light of a variety of wavelengths, HPD photoactivates and becomes cytotoxic.[5,9,10] Singlet oxygen gen-

eration has been identified as the likely mechanism for HPD-induced destruction of murine tumor.[11] Although HPD has absorption maxima at short wavelengths, most experience with photodynamic therapy (PDT) of neoplasms has been with light at or about 635 nm.[12] Recently, HPD was shown to be taken up in plaque but not in normal aortic segments of 4 atherosclerotic rabbits and 1 monkey.[13] The purposes of this study were to confirm selective uptake of HPD within atheroma, to localize the site of uptake of HPD within the atheroma, to demonstrate the potential for PDT of atherosclerosis in the rabbit model.

Methods

Fifteen white male New Zealand rabbits were fed a diet of Purina Rabbit Chow (Ralston Purina Co.) supplemented with 3% by weight of cholesterol (Sigma Co.) dissolved in peanut oil. Feedings continued from 12 to 16 weeks. Five rabbits re-

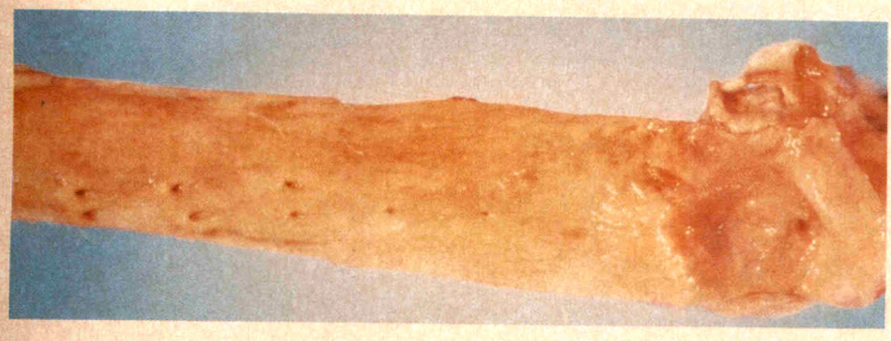

FIGURE 1. Aorta from a control rabbit. The atheroma involvement was graded as smooth and extensive.

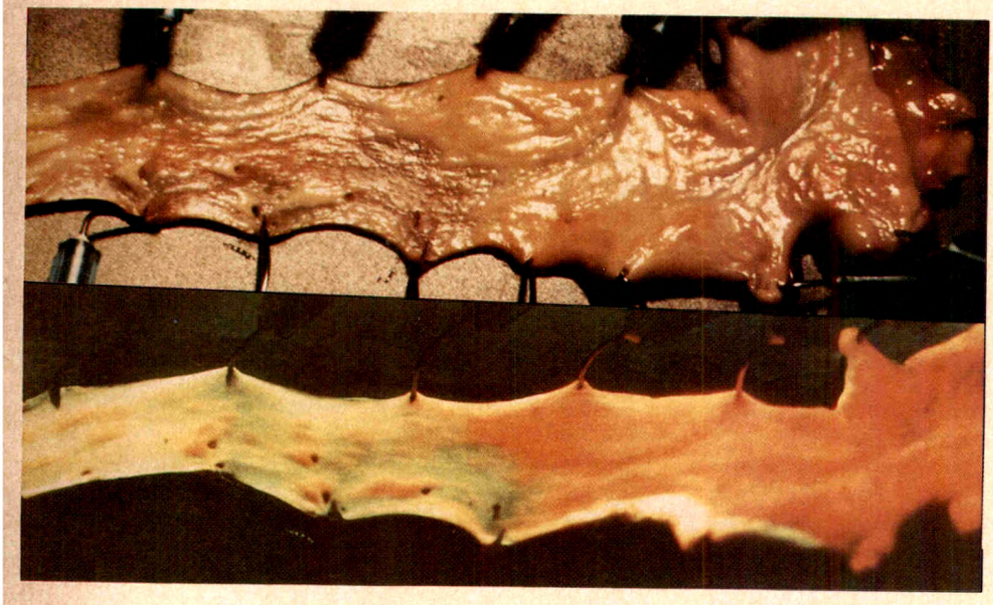

FIGURE 2. A, aorta of a rabbit that received 32 J in the thoracic aorta. The atheroma was classified as minimal and fissured. **B,** the same aorta under a Woods lamp. The atheroma fluoresces orange and the intensity is greatest in the arch and diminishes distally.

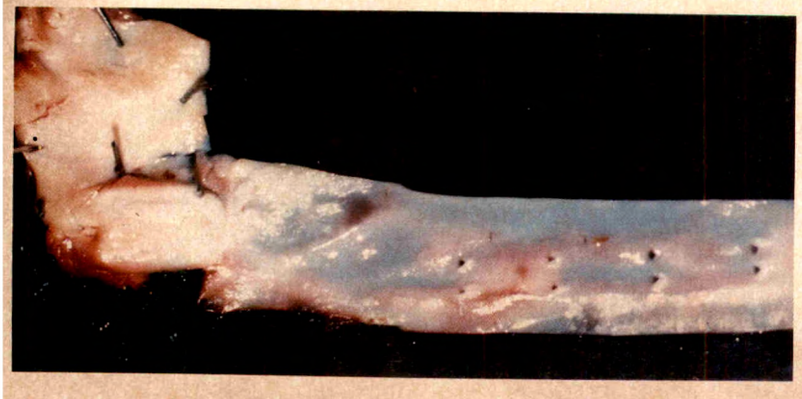

FIGURE 3. Aorta from a rabbit that received 10 mg/kg of hematoporphyrin derivative and 89 J to the thoracic aorta. At 14 days the irradiated zone is atheroma free and glistening.

FIGURE 4. Aorta from a rabbit that received 20 mg/kg of hematoporphyrin derivative and 288 J to the aortic arch. At 14 days the atheroma in the irradiated zone is smooth and extensive.

ceived neither HPD nor PDT. Two rabbits received 10 mg/kg of HPD but no irradiation. These 2 rabbits were killed at 48 and 72 hours after injection. Eight additional rabbits received from 5 to 20 mg/kg of HPD and PDT. These rabbits were killed at 3 hours, 1 week or 2 weeks.

HPD (Photophrin Medical Inc.) was obtained in a concentration of 5 mg/ml. In the 10 rabbits that received HPD, it was injected into an ear vein and then maintained in their regular environment and lighting conditions.

The 636-nm red light used for HPD photoactivation originated from a tunable organic dye laser (Lambda Physik 2000E) filled with a Rhodamine B dye and pumped by a pulsed excimer laser (Lambda Physik 101E). Light was carried from the laser output by 300-μ-core flexible quartz fiberoptic waveguide with an exit divergence angle of 30 to 45°. Pulse duration was 10 ns with a frequency of 40 Hz. Fibertip power output was measured both before insertion of the fiber and at the termination of the irradiation sequence by a laser precision RK 3230 powermeter. Based on measurements obtained at termination of the procedure, the average powers ranged from 12 to 33 mW and yielded peak powers of up to 100 kW. Minimum total energy delivered to the rabbit aortas ranged from 32 to 288 J.

The waveguide was introduced through either the carotid or femoral artery and placed in either the descending thoracic aorta or the arch. Catheter position was determined by transillumination of the chest wall. The dose of HPD, the time to sacrifice after treatment, the site of irradiation and the total energy delivered is shown in Table I. During the period between treatment and sacrifice, the rabbits were fed a regular (nonsupplemented) diet. At necropsy, the aorta was dissected from aortic valves to below the bifurcation, washed with saline solution, opened longitudinally and pinned. It was inspected grossly and photographed with an Olympus OM-1 camera. Each atheroma was classified as either fissured or smooth. The

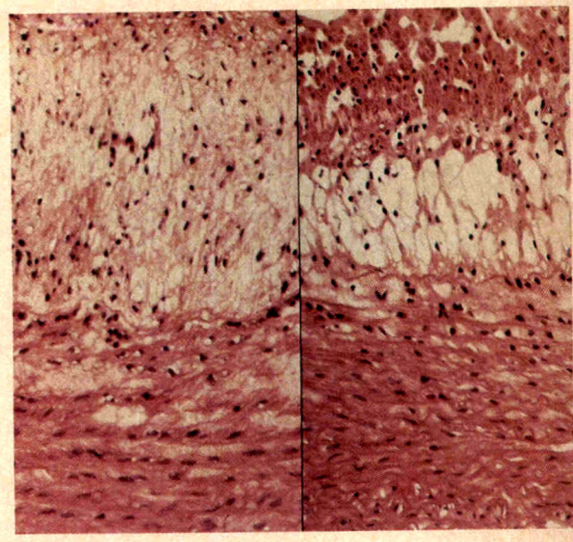

FIGURE 5. A, segment of abdominal aorta. The atheroma has the typical appearance seen in this rabbit model. **B,** segment from the irradiated zone within the aortic arch. Smooth muscle cells have accumulated at the surface of the intima.

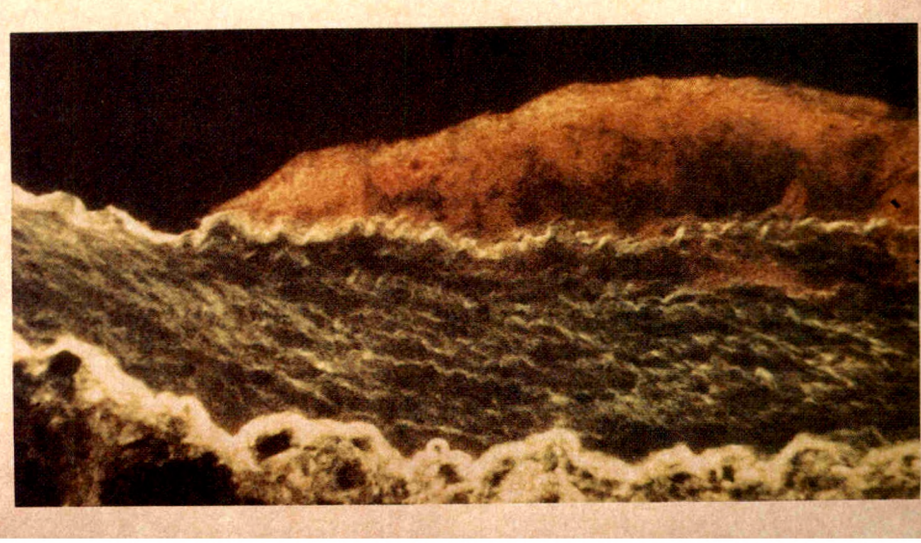

FIGURE 6. Fluorescent photomicrograph from the irradiated segment of aortic arch. The fluorescent intensity diminishes from luminal border to media, indicating a diminishing concentration gradient of hematoporphyrin derivative.

area of intimal involvement was graded as absent, minimal, moderate or extensive. The specimen was then placed under ultraviolet light from a Woods lamp and rephotographed through a Tiffen yellow (minus blue) filter. In addition to the vascular tissues, the gastrointestinal mucosa was also examined under the Woods lamp at necropsy. Specimens of aortic tissue from both irradiated and nonirradiated zones and specimens of lung, liver and kidney were submitted for standard and fluorescence microscopy.

Results

Figure 1 shows the aorta of a control rabbit. The intima is diffusely involved with white atheroma. The atheroma involvement was graded as smooth and extensive.

Figure 2A shows the aorta of a rabbit that received 10 mg/kg of HPD and at 72 hours at least 32 J of laser irradiation with the fibertip positioned just below the arch. The intima was classified as minimal and fissured. The atheroma appears as islands with discrete depressed linear tracks of either normal or near normal intima. Furthermore, the atheroma appears yellow. In no nonirradiated segments did the pattern of atheromatous involvement take on this fissured appearance with yellowing of the plaque.

Figure 2B shows the same aorta under a Woods lamp. The grossly atheromatous area fluoresces orange under ultraviolet light. The intensity of fluorescence is greatest in the arch and diminishes distally. The fissured plaque fluorescences and the areas of greatest fluorescent intensity correspond to thicker plaque. In all rabbits that received HPD, regions of fluorescence corresponded precisely to the presence of gross atheroma. No untreated rabbits exhibited fluorescent atheroma under Woods irradiation.

Figure 3 shows our most striking result. This aorta is from a rabbit that received 10 mg/kg of HPD and at least 89 J of laser irradiation to the thoracic aorta. The rabbit was killed 14 days after irradiation. The proximal portion of the aorta is covered by dense white atheroma. The thoracic aorta is virtually free of atheroma and the intima has a glistening appearance. Even at the origin of the lumbar arteries, a site where we uniformly see atheroma deposition in this model, no atheroma is seen. At the junction zone between the thoracic aorta and the arch, there appears to be small, discrete, broken-up islands of atheroma. Under Woods irradiation the arch of the aorta, which was grossly atheromatous, did fluoresce faintly. No fluorescence was seen over the thoracic aorta.

Figure 4 shows our least striking result. This aorta was taken from a rabbit that received 20 mg/kg of HPD and at least 288 J of laser irradiation in the aortic arch. The area of irradiation over the aortic arch was classified as smooth and extensive.

Figure 5A shows an abnormal aortic segment from the previous rabbit, taken far from the location of the fibertip. The atheroma has the typical appearance seen in this rabbit model. The intima is thickened and diffusely infiltrated by smooth muscle cells. Figure 5B is taken from the aortic arch, which was directly within the zone of irradiation. There is a dense accumulation of smooth muscle cells just at the surface of the intima as opposed to the diffuse infiltration seen in the control segment. This particular histologic characteristic was seen more often, although not exclusively, in irradiated segments.

Figure 6 is a fluorescent photomicrograph of the aortic arch of the same rabbit as is shown in Figure 5. The intima fluoresces orange and the intensity of fluorescence gradually diminishes from the luminal surface toward the media, implying a diminishing HPD concentration gradient. Under higher power examination, the fluorescence was located within the intercellular matrix and the cellular matter of the intima. The green fluorescence is a fluorescence of elastin fibers routinely encountered in this preparation.

In the rabbits that received PDT, no histologic injury was seen in the lungs or liver. Fluorescence microscopy in rabbit 15 revealed some fluorescence within the renal tubules. No cholesterol emboli were seen on histologic examination of any organs.

Table I is a summary of our results. Rabbits 1 through 7 were controls. The area of aortic involvement was always graded as either moderate or extensive, and the atheroma was always graded as smooth. Rabbits 8 through 11 received 10 mg/kg of HPD and thoracic aorta irradiation. Rabbit 8 hemorrhaged and died 3 hours after irradiation. The aortic atheroma was graded as smooth and extensive, indicating no acute laser effect. Rabbits 9 and 10 were killed at 7 days. The atherosclerosis was classified as moderate and minimal, respectively, and both were graded as fissured. Rabbit 11 was killed at 14 days and was our most striking example. Rabbits 12 to 15 received irradiation in the aortic arch. Atherosclerosis in all 3 was classified as smooth and extensive.

Discussion

Our findings demonstrate that HPD, when administered intravenously in rabbits maintained on an atherogenic diet, localizes selectively within atheroma. Atheroma not treated with HPD do not fluoresce under ultraviolet light. The precise topographic correlation between visible atheroma and fluorescence pattern in this study confirms and substantiates the findings of Spears et al,[13] who found fluorescence, but confined their observations to 48 hours after HPD injection. Our study confirms bright fluorescence at 72 hours and shows that fluorescence persists at 1 week, with faint fluorescence at 14 days.

Our findings show that the concentration of HPD is greatest at the intimal surface layers and diminishes toward the media. Although the mechanism of HPD concentration within atheroma is not established, one may speculate based on current knowledge. The smooth muscle cell is recognized as the proliferative cell in atherogenesis.[14–16] In a manner analogous to its uptake in rapidly proliferating tumor cells, HPD could be selectively concentrated within the proliferating smooth muscle cells of atheroma. However, the mucosa of the gastrointestinal tract of our rabbits did not exhibit fluorescence. The mucosal cells of the intestine are among the most rapidly proliferating in the body; therefore, it is unlikely that HPD uptake is related only to the rate of cell proliferation.[17] Localized increase in endothelial cell permeability to lipid is also pivotal in

TABLE I Methods and Results for the 15 Rabbits

Rabbit	HPD (mg/kg)	Energy (J)	Site	Sacrifice	Area	Quality
1					Extensive	Smooth
2					Moderate	Smooth
3					Moderate	Smooth
4					Extensive	Smooth
5					Extensive	Smooth
6	10			48 hrs	Moderate	Smooth
7	10			72 hrs	Moderate	Smooth
8	10	44.8	Thoracic	2 hrs	Extensive	Smooth
9	10	44.8	Thoracic	7 days	Moderate	Fissured
10	10	32.4	Thoracic	7 days	Minimal	Fissured
11	10	89.1	Thoracic	14 days	Absent	
12	5	64.8	Arch	15 days	Extensive	Smooth
13	5	173	Arch	15 days	Extensive	Smooth
14	5	142	Arch	15 days	Extensive	Smooth
15	20	288	Arch	13 days	Extensive	Smooth

HPD = hematoporphyrin derivative.

atherogenesis.[18] Because HPD is lipophilic, it may have moved selectively into atheroma along with lipoprotein molecules. This hypothesis is supported by our finding of diminishing concentration gradient of HPD from luminal surface inward.

A fundamental and insurmountable limitation of our study design was that the delivery of laser energy in a flowing blood stream precluded both precise localization of the impact site and quantitation of the amount of energy delivered to any site on the arterial wall. For this reason we view our results as equivocal as to the potential for PDT. The apparent atherolysis in the thoracic aorta may actually be a reflection of biologic variation in severity of atherosclerosis. Conversely, the apparent lack of effect during aortic arch irradiation may be a result of insufficient sensitivity of our gross anatomic and histologic methods. For example, a 50% reduction in thickness of the plaque of the arch could not have been readily perceived. Our histologic analyses demonstrated differences between irradiated and untreated segments, but these findings were not sufficiently dramatic to be considered unequivocal.

Our mode of laser delivery differed from carcinoma therapy,[6,7] in which the continuous mode is commonly used. In our system the laser was pulsed. The high peak powers achieved with nanosecond pulsing may provide more efficient photoactivation than continuous-mode activation by inducing nonlinear multiphoton processes for HPD activation.[19]

The findings of our study may have several implications. Recent advances in fiberoptic technology have allowed construction of ultrathin flexible endoscopes. Clear images of intravascular structures can be obtained in living animals and in humans.[20] By means of intervascular ultraviolet illumination and HPD, it may be possible to localize atheroma with great precision. Furthermore, serial angioscopic examination may provide a means for sequential observation of a segment after PDT.

We have shown that HPD localizes within rabbit atheroma. The pattern of localization is a continuously diminishing concentration gradient from the endothelial surface toward the media. The HPD is heavily concentrated at 2 days, and persists in diminishing intensity until about 2 weeks. Laser energy delivered through a small-diameter catheter (300 μ) in a flowing blood stream appears to induce gross and histologic changes in some rabbits, although the findings are not consistent.

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Effect of Intracoronary Verapamil on Infarct Size in the Ischemic, Reperfused Canine Heart: Critical Importance of the Timing of Treatment

HUEY-MING LO, MD, ROBERT A. KLONER, MD, PhD, and EUGENE BRAUNWALD, MD

In an effort to determine whether the beneficial effect of calcium blocking drugs occurs only during ischemia or during reperfusion as well, anesthetized dogs were subjected to 3 hours of occlusion of the left anterior descending coronary artery followed by 3 hours of reperfusion. In protocol A, intracoronary verapamil (0.01 mg/kg/min) was begun 90 minutes after coronary occlusion and continued for 1 hour into the reperfusion phase (n = 6) while a control group received an infusion of saline solution (n = 6). In vivo area at risk determined by dye injection was 29 ± 3% of the left ventricle (± standard error of the mean) in the control group and 30 ± 3% in the verapamil group (difference not significant [NS]), whereas the area of necrosis determined by triphenyltetrazolium staining and expressed as a percent of area at risk was smaller in the verapamil group (29 ± 8%) than in the control group (57 ± 8%, $p < 0.05$). In protocol B, verapamil infusion into the left anterior descending coronary was begun 5 minutes before blood reperfusion and continued throughout the 3-hour reperfusion phase. Area at risk was similar in both groups (control, 25 ± 1%, n = 8; verapamil, 28 ± 2%, n = 8 , NS); area of necrosis expressed as a percentage of area at risk was 49 ± 6% in the control group and 45 ± 10% in the verapamil group (NS). Therefore, calcium blockade of ischemic myocytes delays death and enhances salvage produced by reperfusion. However, calcium blockade begun after prolonged coronary occlusion does not enhance reperfusion-induced myocardial salvage.

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Considerable interest has recently focused on the development of techniques for reperfusion of the ischemic myocardium in an effort to limit infarct size.[1–6] Reperfusion must be carried out within a few hours in order to salvage a significant quantity of myocardium.[7] In the clinical realm there is a lag time between the onset of coronary occlusion and successful thrombolysis. It would be useful if the degree of cell death that occurs during this period could be reduced or delayed before reperfusion.

Experimental studies have also raised the question of whether reperfusion exerts a deleterious effect—so-called reperfusion injury.[8] Upon reperfusion after a period of myocardial ischemia, ischemic myocytes gain large quantities of Ca^{++}, as reflected in flux studies, using radioactive Ca^{++} [9,10] and as evidenced by the appearance of intramitochondrial dense bodies containing large quantities of Ca^{++} and by the development of myocardial contracture.[9–12] It has been proposed that the entry of excess Ca^{++} during reperfusion leads to inhibition of mitochondrial energy production, which leads to cell death.[9,13,14] Voltage-dependent calcium channels which can be blocked by calcium entry antagonists are one of the potential routes by which myocytes gain calcium during reperfusion.

There has been considerable interest in the use of calcium channel blocking in protecting ischemic myocardium.[15–17] Some of this interest stems from the concepts of calcium overload that occurs upon reperfusion as discussed herein. The purpose of this study was to determine whether the administration of a calcium blocking drug significantly *after* coronary occlusion enhances reperfusion-induced myocardial salvage. We report the effects of verapamil when administered during the period of induced ischemia and during the first hour of reperfusion, and when administered only during the 3-hour period of reperfusion.

Methods

Mongrel dogs of either sex that weighed 17 to 34 kg were anesthetized with sodium pentobarbital, 30 mg/kg intravenously. The dogs were intubated and ventilated with a Harvard respirator (model 607) at approximately 300 ml of room air/kg body weight/min. The chest was opened in the fifth intercostal space; the pericardium was opened and the heart suspended in a pericardial cradle. A fluid-filled catheter was placed in the left common carotid artery and connected to a Statham P23Db transducer to monitor arterial pressure and heart rate. Catheters were also placed in the left external

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TABLE I Area of Necrosis and Area at Risk

	AR (%)		AN/AR (%)	
	C	V	C	V
Protocol A	29 ± 3	30 ± 3	57 ± 8	29 ± 8*
Protocol B	25 ± 1	28 ± 2	49 ± 6	45 ± 10

* $p < 0.05$ vs control.
AN/AR = area of necrosis/area at risk; AR = area at risk; C = control; V = verapamil.

TABLE II Regional Myocardial Blood Flow (ml min^{-1} g^{-1})

	lep	len	Nep	Nen
Protocol A				
C	0.17 ± 0.09	0.05 ± 0.02	1.48 ± 0.23	1.62 ± 0.21
V	0.21 ± 0.10	0.08 ± 0.06	1.10 ± 0.12	1.25 ± 0.08
Protocol B				
C	0.37 ± 0.11	0.04 ± 0.01	1.56 ± 0.17	1.65 ± 0.19
V	0.25 ± 0.11	0.05 ± 0.02	1.39 ± 0.23	1.62 ± 0.31

C = control; len = ischemic subendocardial zone; lep = ischemic subepicardial zone; Nen = normal subendocardial zone; Nep = normal subepicardial zone; V = verapamil.

jugular vein for intravenous infusion and in the left atrium for injection of radioactive microspheres for measurement of regional blood flow. A long segment of the left anterior descending coronary artery (LAD) was dissected free just distal to the first diagonal branch. After baseline hemodynamic data were recorded, lidocaine, 1.5 mg/kg, was given as an intravenous bolus injection. The LAD was then occluded with an atraumatic Schwartz clamp. Fifteen minutes after occlusion, an injection of radioactive microspheres (8 to 10 μm) was made into the left atrium for measurement of regional myocardial blood flow. The dogs were subjected to 3 hours of coronary occlusion and 3 hours of reperfusion induced by releasing the clamp, and were randomized into a verapamil-treated or a control group at 1 hour after occlusion as follows (Fig. 1).

In protocol A, an intracoronary infusion of verapamil, 0.01 mg/kg/min, into the LAD was begun 90 minutes after occlusion, while the occlusion was maintained for an additional 90 minutes. Verapamil infusion was continued for the first of the 3 hours of reperfusion; a control group of dogs received intracoronary infusion of saline solution. In protocol B, the same dose of intracoronary verapamil infusion (0.01 mg/kg/min) was infused commencing 5 minutes before the onset of reperfusion, i.e., after 175 minutes of occlusion, and was continued throughout the 3-hour reperfusion period. A control group received intracoronary saline solution.

The LAD was cannulated with a 22 gauge intravascular catheter for intracoronary administration of verapamil or saline solution. Cannulation was carried out just before commencing intracoronary infusion and a Harvard pump (model 940) was used for constant intracoronary infusion.

When the experiment was completed, an in vivo area at risk was determined by injecting Monastral blue, 1 ml/kg, into the left atrium with the LAD reoccluded; the heart was then excised. The left ventricle was cut free and then sliced in sections 0.5 cm thick. A clear acetate overlay was placed over the heart slices, and the perfusion defect (myocardium not stained blue, i.e., the area at risk) and the perfused area (myocardium that was stained blue, i.e., the area not at risk) were traced. The heart slices were photographed and then incubated with triphenyltetrazolium chloride to detemine the area of necrosis. Area of necrosis similarly was traced onto an acetate overlay and the heart slices were then photographed. Area at risk and area of necrosis were determined by planimetry using these tracings and corrected for weight of the left ventricular slices. Area at risk was expressed as a percentage of the left ventricle and area of necrosis was expressed as a percentage of area at risk. Hemodynamic data, including heart rate, systolic blood pressure and diastolic blood pressure, were obtained just before occlusion, before drug administration, 1 hour after blood reperfusion, and 3 hours after reperfusion. The investigators were blinded to the results during the study period; specifically, the investigators who determined the area of necrosis and area at risk were not aware of which dogs were treated or which were controls.

Statistical analysis: For paired comparisons, a Student *t* test was used. Hemodynamic data were analyzed by a repeated-measures analysis of variance. Differences were considered significant at the $p < 0.05$ level. Values are expressed as mean ± standard error of the mean.

Results

Fifty-two dogs were entered into the study. Twenty-four dogs were excluded: 16 because of ventricular fibrillation, 3 because of absence of detectable epicardial cyanosis within the first 2 minutes of occlusion, 3 because of poor resolution of the area at risk and 2 because of failure of LAD cannulation. After these exclusions, 12 dogs remained in protocol A and 16 in protocol B.

Area at risk (Table I): Because area of necrosis is a function of area at risk, the area at risk must be compared for each group. In this study, the area at risk was similar between control and verapamil-treated groups in both protocols. In protocol A, area at risk was 29 ± 3% for the control group (n = 6) and 30 ± 3% for the verapamil group (n = 6), NS. In protocol B, area at risk was 25 ± 1% for the control group (n = 8) and 28 ± 2% for the verapamil group (n = 8) (difference not significant [NS]).

Regional myocardial blood flow (RMBF) (Table II): In addition to the gross observation on the development of epicardial cyanosis and contractile abnormality after LAD occlusion, RMBF was assessed 15 minutes after occlusion to assure a comparable ischemic insult in control and treated dogs. In protocol A, the subepicardial blood flow to the ischemic area was 0.17 ± 0.09 for the control group and 0.21 ± 0.10 for the verapamil group, (NS); the subendocardial blood flow in the ischemic zone was 0.05 ± 0.02 for the control

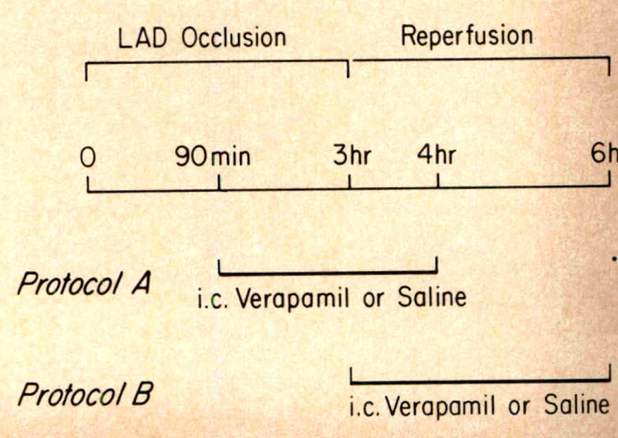

FIGURE 1. Protocols A and B. LAD = left anterior descending coronary artery.

TABLE III Hemodynamic Values

	HR (beats/min)	SBP (mm Hg)	DBP (mm Hg)	DP (mm Hg × beats/min)
Before Occlusion				
Protocol A				
C	148 ± 9	137 ± 11	111 ± 10	19,978 ± 1,672
V	142 ± 3	118 ± 10	92 ± 5	16,888 ± 1,715
Protocol B				
C	163 ± 7	136 ± 6	105 ± 5	22,310 ± 1,759
V	149 ± 6	144 ± 6	111 ± 5	21,586 ± 1,457
Before Treatment				
Protocol A				
C	153 ± 10	135 ± 8	107 ± 9	20,474 ± 1,516
V	139 ± 4	118 ± 7	91 ± 5	16,426 ± 1,425
Protocol B				
C	149 ± 7	128 ± 5	96 ± 6	19,181 ± 1,493
V	144 ± 5	138 ± 7	109 ± 6	19,968 ± 1,404
Reperfusion 1 Hour				
Protocol A				
C	150 ± 9	130 ± 5	102 ± 5	19,460 ± 1,272
V	114 ± 6	108 ± 8	73 ± 7*	12,494 ± 1,488*
Protocol B				
C	138 ± 11	120 ± 3	84 ± 3	16,554 ± 143
V	133 ± 7	125 ± 8	90 ± 6†	16,916 ± 1,871
Reperfusion 3 Hours				
Protocol A				
C	156 ± 10	133 ± 7	105 ± 7	20,718 ± 1,569
V	126 ± 11	117 ± 7	83 ± 6*	14,864 ± 1,410*
Protocol B				
C	131 ± 11	118 ± 3	81 ± 2	15,841 ± 1,984
V	123 ± 8	124 ± 6	84 ± 5†	15,602 ± 1,506

* $p < 0.05$ vs control protocol A.
† $p < 0.05$ vs pretreatment.
C = control; DBP = diastolic blood pressure; DP = double product; HR = heart rate; SBP = systolic blood pressure; V = verapamil.

group and 0.08 ± 0.06 for the verapamil group (NS). Similarly, in protocol B, the subepicardial blood flow in the ischemic zone was similar for both groups (0.37 ± 0.11 in control group and 0.25 ± 0.11 in verapamil group, NS), and the same was true for the ischemic subendocardial blood flow (0.04 ± 0.01 in control group and 0.05 ± 0.02 in verapamil group, NS).

Hemodynamics (Table III): There were no significant differences in heart rate or blood pressure between treatment groups, prior to verapamil therapy. In protocol A, the diastolic arterial pressure and double product in the verapamil group were significantly lower after verapamil than in the control group 1 hour and 3 hours after reperfusion. In protocol B, diastolic blood pressure was decreased in the verapamil group, but the differences between the treated and control groups were not statistically significant.

Area of necrosis/area at risk (Table I, Fig. 2): In protocol A, in which verapamil administration was begun 90 minutes after coronary occlusion, the area of necrosis, expressed as percentage of area at risk, was significantly smaller in the verapamil group (29 ± 8%) than in the control group (57 ± 8%, $p < 0.05$) (Fig. 3 and 4). In contrast, in dogs in which verapamil administration was begun after 3 hours of coronary occlusion, area of necrosis expressed as a percentage of area at risk was not altered by treatment (45 ± 10% for verapamil group and 49 ± 6% for control group, NS).

Discussion

With the widespread use of thrombolytic therapy in the treatment of acute myocardial infarction, it is of interest to determine whether the intracoronary administration of a calcium channel blocker at the time of reperfusion can enhance the myocardial salvage caused by reperfusion. Our results indicate that in the dog, intracoronary verapamil begun after 3 hours of LAD occlusion and at the time of coronary reperfusion did *not* provide additional myocardial salvage. However, intracoronary verapamil begun during the ischemic period, even in a delayed fashion, i.e., 90 minutes after occlusion, enhanced substantially the myocardial salvage achieved by reperfusion. These results suggest that the intervention of calcium blockade at the time of reperfusion does not salvage ischemic myocardium. The results support the concept that at the end of the period of ischemia, all myocardial cells that are destined to die are already irreversibly injured and that reperfusion per se does not increase the number of cells which die. Nevertheless, we cannot rule out the possibility that other agents may be beneficial when administered during the reperfusion phase.

Although the mechanism of the observed myocardial salvage is not known, it is postulated that a substantial population of mildly, reversibly injured subepicardial myocytes is present at 90 minutes after occlusion compared with that at 3 hours. Most of the calcium channels of these myocardial cells are presumably still functioning and can still be blocked by verapamil. In a study using voltage clamp techniques, diltiazem exerted a more profound calcium channel blocking action on ventricular myocardium at a potential of −61 mV than of −120 mV.[18] Thus, calcium antagonists may exert a greater blocking effect on ischemic than normal myocytes because the former have a decreased resting membrane potential.[19] This would exert an antiischemic

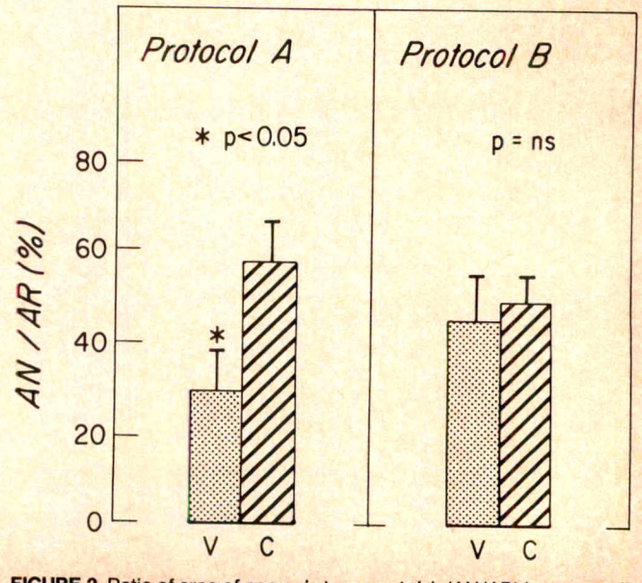

FIGURE 2. Ratio of area of necrosis to area at risk (AN/AR) in verapamil (V) groups (**stippled bars**) and control (C) groups (**striped bars**) of protocols A and B.

action and minimize energy expenditure of cells that were only reversibly injured. In accord with this hypothesis, Smith et al[20] showed that verapamil exerts a selective depression of function of the ischemic myocardium, and thereby presumably exerts a more potent protective effect in these cells. Serruys et al[21] reported that regional administration of nifedipine had a direct negative inotropic effect on the myocardium suggesting it might spare regional O_2 consumption. Furthermore, decreased calcium influx into ischemic myocardium preserves both mitochondrial function and ultrastructure with subsequent preservation of myocardial ATP.[22–26] Nayler et al[27] showed that when verapamil was added to the perfusate at the very start of hypoxic perfusion of isolated guinea pig hearts, it attenuated the hypoxia-induced increase in resting tension (contracture). However, when this calcium antagonist was added only *after* the start of hypoxia, when resting tension already had begun to increase, it failed to diminish this increase in resting tension. Similarly, Klein et al[17] showed that in the pig heart rendered ischemic for 75 minutes and then reperfused for 4 hours, pretreatment with diltiazem reduced infarct size beyond the reduction achieved by reperfusion, whereas diltiazem begun during ischemia had a smaller and statistically insignificant effect.[17]

The mechanism of the salutary action of verapamil may also have been related to its systemic hemodynamic action as well as to its effect on calcium entry into ischemic myocytes. Thus, in protocol A, the verapamil-treated dogs had significantly lower diastolic pressures and systolic pressure–heart rate products, both after 1 and 3 hours of perfusion, than control dogs. These factors may have contributed to a lowering of myocardial oxygen demand during ischemia.

When verapamil was infused after 3 hours of ischemia, no enhancement of myocardial salvage occurred. Presumably, at this time it did not have the opportunity to exert an antiischemic effect on myocytes, which were already irreversibly damaged and which became necrotic despite reperfusion.

The dosage of verapamil we chose for intracoronary administration is comparable to that used systemically in patients. The purpose of intracoronary administration was to maximize the potential for myocardial salvage. In our pilot studies, this dosage and route of administration were well tolerated, but it is close to maximal, since 2:1 atrioventricular block developed when the dose was doubled.

The action of calcium channel blockers in enhancing reperfusion-induced myocardial salvage is probably not unique. Indeed, we have observed that timolol,[28] a β-adrenergic blocking drug, and esmolol,[29] an ultrashort-acting β-blocking drug, when given soon after coronary occlusion, can substantially augment reperfused-induced salvage of ischemic myocardium.

In the present study, infarct size was assessed by the triphenyltetrazolium chloride technique. This tech-

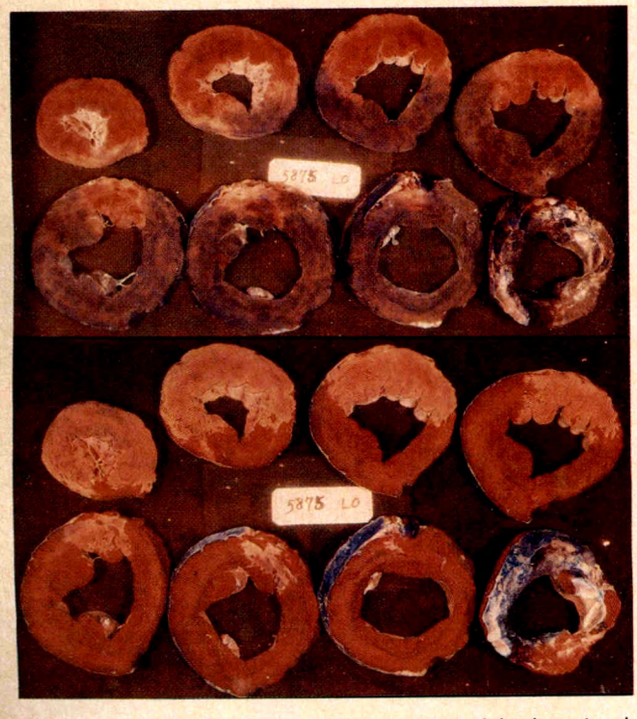

FIGURE 3. Top, left ventricular slices from a control dog in protocol A showing the nonischemic area (blue) and unstained pink area at risk. **Bottom,** left ventricular slices from the same dog as in panel A after incubation in triphenyltertazolium chloride. The infarct appears as the pale tissue and corresponds closely to the area at risk.

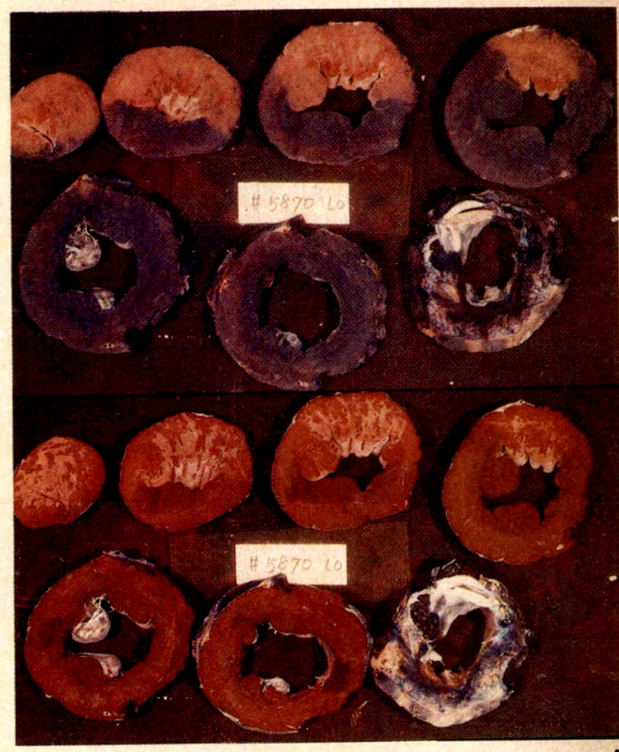

FIGURE 4. Top, left ventricular slices from a verapamil-treated dog in protocol A showing the nonischemic area (blue) and unstained **pink** area at risk. **Bottom,** left ventricular slice from the same dog as in panel A after incubation in triphenyltetrazolium chloride. The infarct appears as the pale tissue and is much smaller than the area at risk and smaller than the infarct shown in Figure 3B. While most salvage occurs in the subepicardium, there are areas where salvage (noninfarcted tissue within the risk zone) appears along the lateral edge of the infarct. This is most apparent in the third ventricular slice from the apex.

nique reliably localizes and sizes infarcts early after myocardial ischemia.[30–34] In our laboratory, infarcts assessed by triphenyltetrazolium chloride have shown good correlation to infarct size assessed by histologic examination and electronmicroscopy.[32] Schaper[33] stated, "The tetrazolium method, when used without reperfusion, becomes discriminative between 3 and 4 hours after coronary occlusion and it can be trusted at about 6 hours after occlusion. With reperfusion, infarcts can be demonstrated after only 20 min of occlusion." Fishbein et al[30] also showed that this technique is valid for localizing irreversibly injured myocardial cells, assessed by cardiac ultrastructure, as early as 3 to 6 hours after coronary occlusion.

The area at risk technique used in the present study is an in vivo technique; that is, it defines a zone of low blood flow at the time of coronary artery occlusion. Since the marker is infused in vivo during coronary artery occlusion, it takes into account coronary collateral blood flow and results in a physiologic perfusion defect of low blood flow much like a thallium scan. This technique has been used in previous studies by this laboratory[35] and in a permanent coronary occlusion model results in a relatively high percentage of necrosis to area at risk.[35] Data derived from in vivo dye injection are similar to those derived from injection of microspheres with subsequent autoradiography.[16] In contrast, risk areas measured by in vitro techiques (injection of barium gel into the coronary arteries or in vitro infusions of dyes down opposite coronary beds simultaneously and under the same pressures) define an anatomic coronary bed at risk that does not take coronary collateral flow into account. We believe that the in vivo technique is more physiologic and more accurately reflects the status of the coronary vasculature as it might occur in man during an acute occlusion, because coronary perfusion pressure distal to the occlusion is always less than that in the nonoccluded bed. Furthermore, we have found that when both in vivo and in vitro techniques are assessed in the same animal,[36] the extent of necrosis is more closely defined by the in vivo rather than the in vitro risk region. The ratio of area of necrosis to area at risk was always lower when the in vitro technique was used. Hence, the in vitro area at risk may actually overestimate the amount of tissue actually at risk for developing necrosis.

In conclusion, although ischemic myocardium can be reperfused by thrombolysis in an emergency setting in many patients with evolving myocardial infarction, a significant delay is unavoidable before thrombolysis is achieved, particularly when the thrombolytic agent is administered by the intracoronary route. The onset of irreversible injury may be delayed by early therapy with a calcium channel blocker, and this may enhance the salvage of tissue at the time of later reperfusion. However, when *both* the administration of the calcium channel blocker and reperfusion are delayed beyond a critical point, the drug is unlikely to enhance the quantity of myocardium salvaged by reperfusion.

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Sudden Death and Experimental Acute Myocardial Infarction

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Acute myocardial ischemia was produced by ligature of the anterior descending coronary artery on 658 dogs in 3 separate laboratories. Overall, 12% of the dogs died within the first hour (instantaneous death) and 25% within the first 24 hours (sudden death). The sudden death rate was significantly related to the logarithm of the weight of the dogs in the range studied. It varied widely if values from small series, comprising the same number of dogs, were considered. Values became less dispersed as the size of the series increased. In series of 10 dogs, sudden death rates ranged from 0 to 70%, whereas in series of 100 dogs the range was 14 to 36%. Stable values were obtained for 50 to 60 dogs per series. Accordingly, reliable assessment of preventive measures can be made only with experimental series of at least this size.

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Sudden death has been defined by the World Health Organization as death resulting from an event occurring within 24 hours of the onset of an acute episode. Death within 1 hour of the onset of an acute event is called instantaneous death. This distinction is not always clearly made. In industrialized countries, 1,500 persons per million inhabitants die suddenly each year. Sudden cardiac death remains the "major challenge confronting contemporary cardiology." [1] Accordingly, much research has been done in this area.[2–4] The development of drugs with efficient preventive properties relies on the availability of suitable experimental models. Among those proposed by Moore and Spear,[5] the model that comes closest to human pathologic conditions appears to be acute ischemia created by ligature of a coronary artery.

Ligature of the anterior descending coronary artery in the dog sometimes brings about immediate rhythm disorders, and in some cases fatal ventricular fibrillation. Surviving dogs later display ventricular arrhythmia, which peaks 17 to 24 hours after arterial occlusion. This period is usually chosen for the study of antiarrhythmic agents. However, some investigators have used this model to study preventive treatment using pharmacodynamic drugs, although under these conditions, mortality is somewhat haphazard.[6] Most experimental series are too small to allow valid statistical treatment, so the experimental results are of limited value. The aim of this work was to determine the size of the experimental group required to obtain reproducible results, and thereby to determine the number of dogs needed to assess confidently the preventive value of a pharmacodynamic agent with regard to sudden death resulting from coronary occlusion. Sudden and instantaneous deaths were distinguished, and any influence of weight and sex, and of season on mortality was sought.

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Methods

This work involved 658 mongrel dogs of either sex. One-stage coronary ligature was carried out using an identical procedure initially developed in laboratory I (Clermont-Ferrand) and extended to laboratory II (Rennes) and laboratory III (Riom). One hundred forty-eight dogs (mean weight

TABLE I Effects of Coronary Ligature in the Dog During the First 24 Hours

	I		II		III		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Instantaneous death (1 hour)	15	(10)	36	(12)	31	(15)	82	(12)
Sudden death (24 hours)	29	(20)	87	(29)	46	(22)	162	(25)
Ectopic beats at 24 hours	114	(77)	215	(71)	142	(69)	471	(71)
No ectopic beats at 24 hours	5	(3)	1	(0.3)	19	(9)	25	(4)
Total	148		303		207		658	

Laboratory I—Clermont-Ferrand; II—Rennes; III—Riom. n = number of dogs.

15.7 ± 0.3 kg) underwent operation in laboratory I, 303 (19.6 ± 0.3 kg) in laboratory II and 207 (11.2 ± 0.1 kg) in laboratory III. The study lasted about 5 years.

A tracheal intubation was performed under general anesthesia (sodium pentobarbital, 6 mg/kg, and chloralose, 80 mg/kg, i.v.). Each dog was artificially ventilated with room air (Braun pump). The thorax was opened in the fourth left intercostal space. After incision of the pericardium the heart was placed in a pericardial cradle to facilitate dissection of the anterior descending coronary artery, which was tied in 1 stage 1 cm from its root. The pericardial cradle was then detached, the pericardium closed with a few stitches, and the thorax finally stitched up in 3 planes.

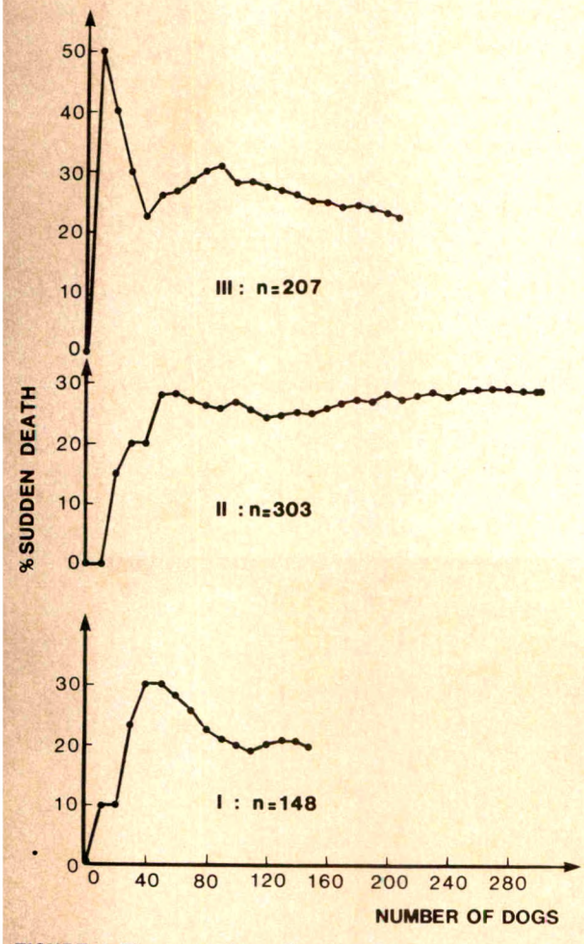

FIGURE 1. The percentage of sudden deaths is proportional to the logarithm of the weight of the dogs: % = 52.85 log weight − 40.76. The regression line was calculated from the percentages of sudden death (**dots**) observed for the following weight ranges: 5 ≤ weight (kg) <13; 13 ≤ weight (kg) <21; 21 ≤ weight (kg) <29; 29 ≤ weight (kg) ≤41.

The variability of occurrence of sudden death was studied as follows. First, the death rate in ligatured dogs was calculated as a percentage in each of the 3 laboratories for the first 10 dogs, the first 20 dogs, the first 30 dogs, and so on. Then, the minimum, maximum and mean death rates were calculated as percentages for experimental series containing 10, 20, 30, and so on, up to 100 dogs successively ligatured. The series were made up by taking the first dog operated on as dog 1 in series 1, the second dog operated on as dog 1 in series 2 and so on. For example, in the first study (laboratory I, 148 dogs) there were 139 series of 10 dogs, 129 series of 20 dogs, and so on. Finally, the confidence intervals determining the theoretical number of survivors needed to indicate that a drug being tested has preventive action, were calculated as a function of the number of animals per series.

The statistical calculations were carried out, depending on the case, by the Student t test in unpaired series, and by 1-factor analysis of variance. Comparison of percentages was made by calculation of reduced deviations.

Results

Study of death rate: Death rates are listed in Table I. Of the whole set of 658 dogs, 82 (12%) died within the first hour (instantaneous death). Instantaneous death rates were not significantly different among the 3 laboratories: 10%, 12% and 15% in laboratories I, II and III. One hundred sixty-two dogs, (25%) died within the first 24 hours (sudden death). Sudden death rates in laboratory I (20%) and laboratory II (29%) differed significantly, but not between laboratory III (22%) and either of the 2 laboratories.

Complete absence of rhythm disorders 24 hours after ligature was observed, on average, in 4% of the total population and in 5% of the surviving dogs. Distribution among the 3 populations varied widely; 3%, 0.3% and 9% of all the dogs, and 4, 0.4 and 11% for surviving dogs in laboratories I, II and III, respectively.

Influence of weight: The influence of weight was studied for the dogs involved in the experiments in laboratories I and II only. Of the 451 dogs considered (mean weight 18.4 ± 0.3 kg), 116 died within 24 hours of ligature. There was a significant difference between the mean weight of the surviving dogs (17.7 ± 0.3 kg) and that of the dogs that died suddenly (20.6 ± 0.5 kg). In general, the percentage of sudden death cases is proportional to the logarithm of the weight of the dogs: % = 52.85 log weight −40.76 (Fig. 1). The difference in the percentage of sudden death between laboratories

TABLE II Study of Death Rate: Percentages According to Sex

Laboratory	Female			Male		
	Operated Dogs	Died	%	Operated Dogs	Died	%
I	78	14	18	69	14	20
II	106	30	28	197	57	29
I + II	184	44	24	266	71	27

Laboratory I—Clermont-Ferrand; II—Rennes.

TABLE III Study of Death: Percentages According to Season

Season	I			II			III			Total		
	Operated Dogs	Died	%	Operated Dogs	Died	(%)	Operated Dogs	Died	%	Operated Dogs	Died	%
Winter	38	10	26	53	14	26	47	13	28	138	37	27
Spring	47	8	17	102	25	24	48	9	19	197	42	21
Summer	24	4	17	67	29	43	58	14	24	149	47	31
Autumn	39	7	18	81	19	23	54	10	20	174	36	21

Laboratory I—Clermont-Ferrand; II—Rennes; III—Riom.

I and II would be a result of the difference in the weight of the dogs: respectively, 15.7 ± 0.3 kg and 20% sudden death, and 19.6 ± 0.3 kg and 29% sudden death.

Influence of gender: Gender had no influence on death rate (Table II).

Influence of season (Table III): Season did not affect death rate in the series of laboratories I and III. However, in laboratory II, death rate in dogs operated on in summer was significantly different from that in dogs operated on in autumn and spring. The weight of the dogs is irrelevent; the mean weight of the 67 dogs operated on in summer was 21.9 ± 0.6 kg and that of the 81 dogs operated on in autumn was 21.8 ± 0.7 kg.

Variability of occurrence of sudden death: *Death rate as a function of the number of dogs successively operated on* (*Fig. 2*): For the first 10 dogs ligatured, the percentage death rate varied widely: 10% for laboratory I, 0% for laboratory II and 50% for laboratory III. From the 30th dog, this variable tended to become stable. Thus, for laboratory I, from the 30th to the 148th dog, the percentage varied between 19 and 30% (mean 20%). In laboratory II, from the 30th to the 303rd dog, the death rate varied between 20 and 29% (mean 29%). In laboratory III, from the 30th to the 207th dog, the death rate varied from 22 to 31% (mean 22%). Overall, the death rate varied between 19 and 31% from the 30th dog onward.

Variability of the death rate as a function of the number of dogs per experimental series (*Table IV*): After coronary ligature performed successively on series of 10, 20, 30, and so on, up to 100 dogs, the spread of the percentage of sudden deaths narrowed as the number of dogs per series increased. Thus, for series of 10, 50 and 100 dogs, the spread was, respectively, 0 to 70%, 8 to 32% and 14 to 23% in laboratory I, 0 to 60%, 18 to 38% and 22 to 36% in laboratory II, and 0 to 50%, 12 to 38% and 15 to 28% in laboratory III.

Overall, from 50 to 60 dogs per series onward, minimum death rates stabilized between 8 and 14% and maximum death rates between 38 and 35%.

Number of survivors theoretically necessary to demonstrate preventive action of a drug (Table V): This variable was calculated for $p = 0.05$ and $p = 0.001$ as a function of the number of dogs per series. For $p = 0.05$, no significant result is possible from a group of only 10 dogs. At least 40 dogs per group are needed to assess preventive activity confidently.

Discussion

The death rate in dogs after ligature of the anterior descending coronary artery reportedly varies from 0 to 50% (Table VI). However, the number of dogs involved has usually been small, which explains the wide spread. Michelson et al[6] mentioned the wide variability of occurrence of ventricular fibrillation 30 minutes after ligature in 90 dogs with mean death rate 37%. Grimal et al[11] found a 22% death rate after 24 hours in dogs in which 1-stage ligature had been performed (93 dogs), and a 20% death rate when ligature had been carried out in 2 stages (218 dogs) as advocated by Harris and Kokernot.[17]

Wide disparity of results owing to an insufficient number of dogs was evident. Death rate among the first

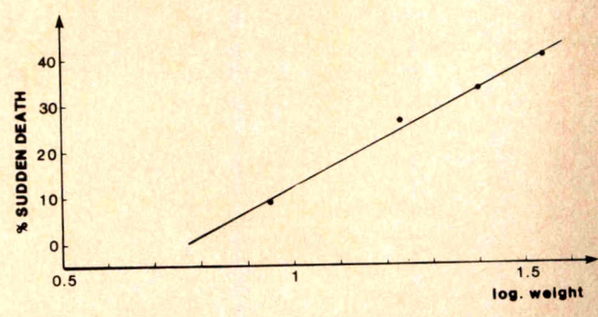

FIGURE 2. The percentage of sudden deaths varied according to the number of dogs successively ligatured. From the 30th dog this parameter tends to become stable. Laboratory I—Clermont-Ferrand; laboratory II—Rennes; and laboratory III—Riom.

TABLE IV Variability (Percent) of Sudden Death According to Number of Dogs Per Series

No. of Dogs Per Series	I (n = 148) % Sudden Death			II (n = 303) % Sudden Death			III (n = 207) % Sudden Death			Total Results % Sudden Death		
	Min.	Max.	Mean	Min.	Max.	Mean	Min.	Max.	Mean	Min.	Max.	Mean
10	0	70	21	0	60	29	0	50	21	0	70	25
20	5	55	21	10	45	29	5	45	22	5	55	25
30	7	43	21	17	47	29	10	40	22	7	47	25
40	5	37	20	17	37	30	12	37	22	5	37	25
50	8	32	19	18	38	30	12	38	23	8	38	25
60	8	28	18	20	37	30	15	33	23	8	37	25
70	10	26	18	20	36	29	16	33	23	10	36	25
80	14	24	18	20	35	29	16	30	23	14	35	25
90	14	22	18	22	35	29	14	31	23	14	35	26
100	14	23	19	22	36	19	15	28	23	14	36	26

Laboratory I—Clermont-Ferrand; II—Rennes; III—Riom. n = number of operated dogs.

TABLE V Theoretical Number of Surviving Dogs After Coronary Ligature to Define Preventive Activity of Drugs

No. of Pretreated Dogs Per Series	p = 0.05		p = 0.001	
	Theoretical % Sudden Deaths	Min. Theoretical No. of Surviving Dogs	Theoretical % Sudden Deaths	Min. Theoretical No. of Surviving Dogs
10	...*	...*	...*	...*
20	6.2	19	...*	...*
30	9.8	27	...*	...*
40	12	35	3	39
50	13.3	43	5.2	47
60	14.4	51	6.9	56
70	15.2	59	8.3	64
80	16	67	9.5	72
90	16.7	75	10.6	80
100	17.3	83	11.5	89

* The number of pretreated dogs was insufficient for this significance level.

TABLE VI Death After Ligature in One or Two Stages of Anterior Descending Coronary Artery

Authors	No. of Operated Dogs	Death (%)
Ligature in 1 Stage		
Smith[7]	11	9
Manning et al[8]	17	10
	22 (awake)	40
Harris[9]	50	50
Chardach et al[10]	22	4.5 (24 hours)
Grimal et al[11]	93	22 (24 hours)
Lown and Wolf[12]	32 (awake)	53
Marshall & Parratt[13]	14	35
Davis & Bigger[14]	15	40
Chew et al[15]	14	29
Michelson et al[6]	90	37
Kanamaya et al[16]	24	50 (30 min)
Ligature in 2 Stages		
Harris & Kokernot[17]	25	0
Harris[18]	32	25–33 (72 hours)
Clark & Cummings[19]	92	6
Hood et al[20]	28	21.4
Grimal et al[11]	218	20 (24 hours)
Michelson et al[21]	10	0 (2 hours)

10 dogs to be ligatured was 10% in laboratory I, 0% in laboratory II and 50% in laboratory III. Overall, for series of 10 dogs sudden death rate can vary from 0 to 70% and for series of 20 dogs from 5 to 55%.

This disparity readily explains the wide variability of results reported for preventive activity assessment of drugs. Yenikomshian and Lown[22] claimed that lidocaine had an antifibrillatory effect. They observed, in 18 dogs treated with lidocaine, a 33% fibrillation rate, compared with 72% in 18 control dogs. This result was not reproduced by Marshall and Parratt,[13] who observed a 34% death rate in 14 control dogs and a 25% death rate in 12 dogs receiving treatment. Similarly, Naito et al[23] found a 49% death rate in 61 controls and 37% in 19 treated animals. Similar results were observed with amiodarone treatment. Chew et al[15] reported an antifibrillatory effect of amiodarone. They found a 29% ventricular fibrillation rate in 14 control dogs and a 9% rate in 11 treated dogs. However, Naito et al[23] found a 44% death rate in 18 treated dogs and a 49% rate in 61 controls. In view of these results, the validity of the positive results reported for bepridil[24] (20 controls, 10 treated dogs), propranolol[16] (24 controls, 24 treated dogs), and the comparison of phenytoin and bretylium tosylate[22] (18 controls and, respectively, 10 and 12 treated dogs) may be doubted. Using 15 controls and 15 treated dogs, Davis and Bigger[14] attempted to evidence an increase in sudden death rate due to thioridazine.

In conclusion, for reliable assessment of potential preventive agents for sudden death, at least 50 dogs per experimental series are essential. Dogs of similar weight should be chosen because larger dogs are more vulnerable to ventricular fibrillation than smaller ones. Gender appears irrelevent; season may have a slight effect on death rate.

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Effect of Pulmonary Artery Distention on Systemic Vascular Resistance in Newborn Lambs

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Balloon distention of the left pulmonary artery (PA) was produced in 14 lambs (aged 1 to 3 days) to assess whether an increase in systemic vascular resistance results from such distention. The lambs were anesthetized with chloralose and instrumented to enable measurement of systemic blood flow, PA pressure, aortic pressure, heart rate and right atrial pressure. PA distention resulted in an increase in systemic vascular resistance and aortic pressure ($p < 0.05$). This result was probably due to a systemic vasoconstrictor response, since systemic blood flow and right atrial pressure did not change significantly. Limited trials using autonomic blocking agents suggested that the response is either a reflex under autonomic control or a response to humoral release of α-adrenergic substances. In conclusion, some interdependence appears to exist between the systemic and pulmonary vascular beds. It is postulated that such changes may be important in fetal life when they may affect redistribution of cardiac output during adaptation to hypoxemia.

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Distention of the pulmonary artery (PA) results in a significant increase in PA pressure distal to a distending balloon in animals and in humans.[1–3] In addition, distention of the PA of adult animals causes variable reflex effects on the systemic circulation.[4,5] Increased systemic vascular resistance (SVR) has been observed[6–8] in some infants with persistent fetal circulation, a syndrome of central cyanosis due to extrapulmonary right-to-left shunting, caused by pulmonary hypertension.[9–11] This study establishes whether acute PA distention can cause increases in SVR in newborn lambs.

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Methods

Studies were performed in 14 newborn lambs (aged 1 to 3 days). The lambs were anesthetized with intravenous alpha chloralose (40 mg/kg body weight), underwent tracheotomy, and were ventilated with a Harvard animal ventilator. Arterial blood gases were maintained in the physiologic range (pH 7.35 to 7.45, P_{O_2} 60 to 90 torr, P_{CO_2} 35 to 45 torr). A left thoracotomy was performed and the ductus arteriosus was isolated and divided. Dissection of tissues surrounding the main PA and its bifurcation was minimized to avoid disruption of sur-

rounding neural elements. The lambs were instrumented to enable measurement of systemic blood flow, using an electromagnetic flow probe on the ascending aorta, and aortic and right atrial pressures using fluid-filled catheters. The flow probe was positioned to avoid impingement on the PA. In addition, an end-hole cuffed balloon catheter was placed in the main PA and advanced to place the balloon in the left PA to enable distention along with PA pressure measurement distal to the balloon. Balloon position was confirmed by palpation.

The flow probes were calibrated using standard flows of normal saline solution generated by a roller flow pump and measured with a graduated cylinder. The pressure transducers were calibrated using a mercury manometer. The 0 reference was taken at the midchest level with lambs in a lateral decubitus position.

The flow and pressure signals were recorded on a Hewlett-Packard eight-channel strip-chart recorder for inspection and calibration purposes. The mean analog flow and pressure signals were processed by an analog-to-digital converter of a microcomputer system (IMSAI 8080), which increased the sensitivity of our system 5-fold. Resistance calculations were performed using the classic equation for resistance where SVR is equal to the mean aortic pressure minus the mean right atrial pressure divided by the mean systemic blood flow. Results were displayed on a video monitor every 0.5 second.

Normal saline solution (1 to 1½ ml) was used to inflate the catheter balloon for 2 to 5 minutes to distend the left PA. The maximal changes in mean PA pressure, mean aortic pressure, mean right atrial pressure, mean systemic blood flow and SVR were assessed using the baseline and peak changes tabulated from the video monitor. Results are expressed as mean ± standard deviation. Statistical analysis was performed using 2-tailed paired t tests with each lamb serving as its own control.

We performed limited trials using α- or β-autonomic blockade or vagotomy in responsive lambs to establish whether the observed changes were under reflex autonomic control. In 1 lamb, after assuring adequate β-adrenergic blockade, distention of the PA was repeated. Adequate blockade was confirmed using a heart rate dose-response curve to isoproterenol with subsequent blockade with propranolol. This was followed by right and left vagotomies. In 2 additional lambs, after assuring adequate α-adrenergic blockade, distention of the PA was repeated. Adequate blockade was confirmed using blood pressure dose-response curves to norepinephrine with subsequent blockade with phenoxybenzamine.

Results

During 48 trials (1 to 7/lamb), distal PA pressure increased with no decrease in systemic blood flow. Additional trials in which distal PA pressure, heart rate or systemic blood flow decreased were not included in the

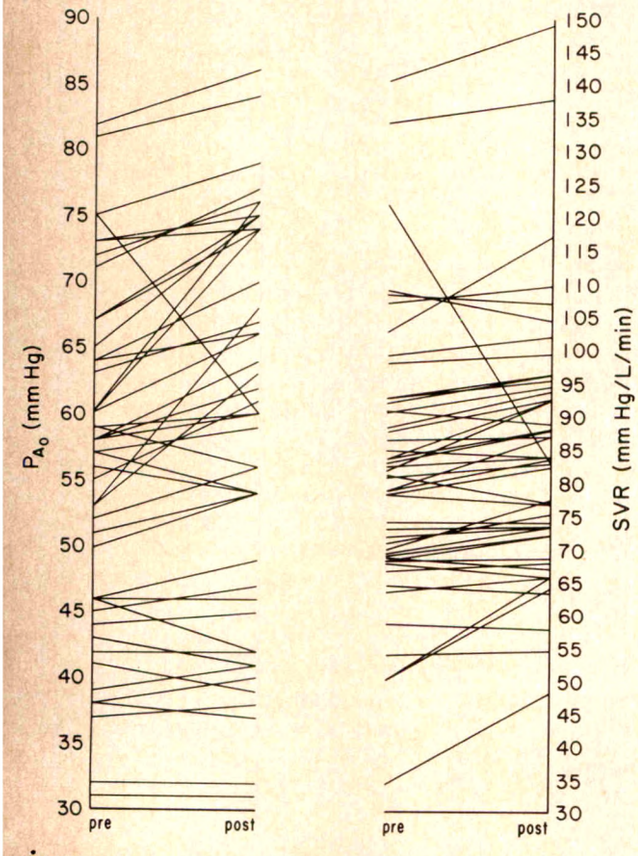

FIGURE 1. Paired pre- and postaortic pressure (PA_0) and systemic vascular resistance (SVR) changes after balloon distention of the pulmonary artery in 48 trials are connected by **solid lines.** Identical data are present in several pairs of PA_0 changes; thus, only 46 lines appear. In 1 trial performed before baseline stabilization, the paired aortic pressure and paired SVR changes decreased strikingly. Four subsequent trials in the same preparation showed increases in 2 and decreases in 2 in PA_0 and SVR from the stabilized baseline. The data were all included in the paired data analysis. The decreases in the latter 2 trials as well as in other trials were less striking and were attributed to biologic variability.

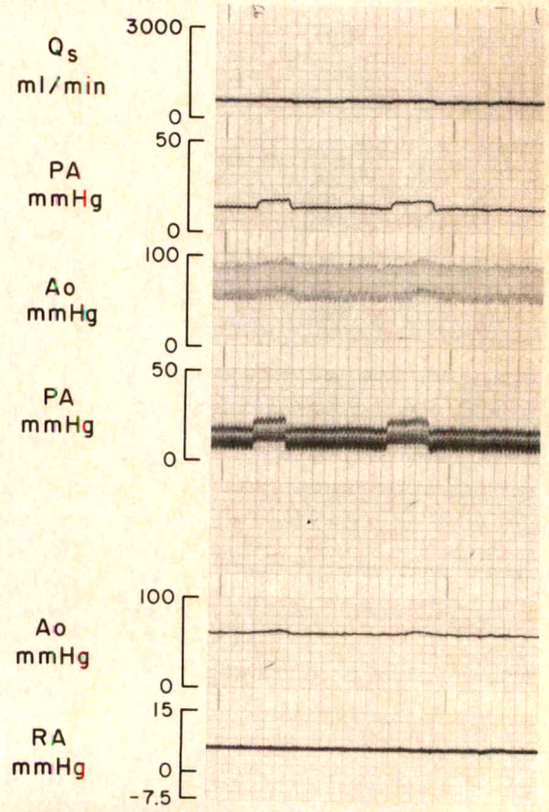

FIGURE 2. Pressure and flow tracings from 1 lamb subjected to left pulmonary artery balloon distention. The distal pulmonary artery pressure (PA) and aortic pressure (Ao) increased and systemic flow (Qs) and right atrial pressure (RA) did not change. Both pulsatile and mean aortic and pulmonary artery pressure tracings are recorded.

analysis because these were interpreted to indicate PA obstruction. After distention of the PA, SVR and aortic pressure increased significantly when the data were analyzed by paired t tests ($p < 0.05$) with each lamb serving as its own control (Fig. 1). However, mean SVR (81.8 ± 20 mm Hg/liter/min to 84.4 ± 19 mm Hg/liter/min) and mean aortic pressure (55.5 ± 13 mm Hg to 58.2 ± 15 mm Hg) did not change significantly because of the wide variation between lambs. The mean baseline systemic blood flow was 0.69 ± 0.3 liters/min and the mean right atrial pressure was 2.7 ± 2 mm Hg. Changes in these variables after PA distention were not statistically significant (Fig. 2).

The baseline mean distal PA pressure of 18.9 ± 7 mm Hg increased to 25.6 ± 9 mm Hg ($p < 0.05$). Pulmonary vascular resistance was not assessed because left atrial pressure and pulmonary blood flow were not measured.

In the lamb treated with β blockade, after distention of the PA, the systemic vascular response persisted. Right vagotomy did not obliterate the response, but a subsequent left vagotomy did. In the additional lambs treated with α blockade, incomplete blockade was initially present (Fig. 3). Once complete blockade was confirmed, PA distention did not result in SVR changes. In addition, the distal PA pressure changes were blocked (Fig. 4).

Discussion

Acute PA distention caused increases in SVR in newborn lambs, which appeared to be a result of systemic arterial vasoconstriction since systemic flow and right atrial pressure did not change.

Our findings are similar to those observed by others in anesthetized adult dogs subjected to balloon distention of the pulmonary trunk.[5] In other studies reporting variable responses in systemic arterial pressure, resistance changes were not calculated.[4] The latter investigators found the responsible baroreceptors to be much more concentrated in the pulmonary arterial branches than in the main PA.[12] This is consistent with our experience. In another study, both conscious and anesthetized dogs were evaluated.[3] A small increase in

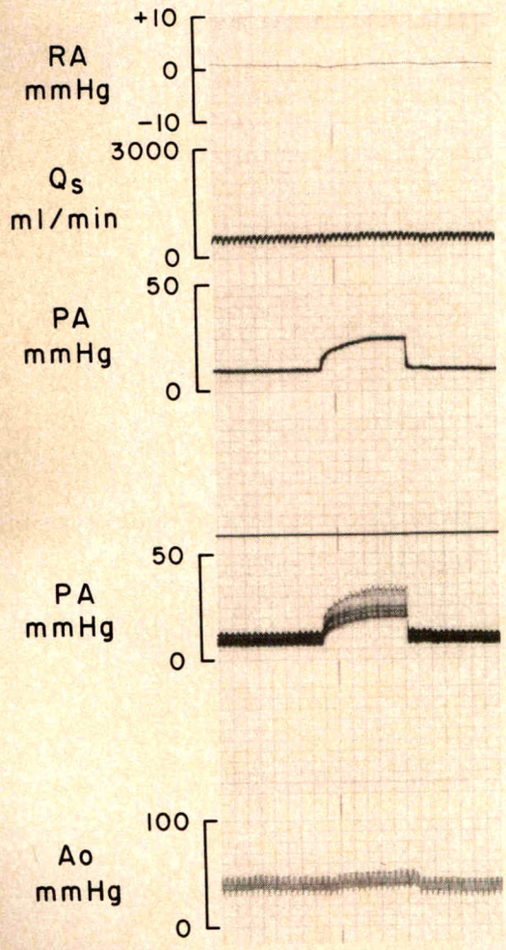

FIGURE 3. Right atrial (RA), pulmonary artery (PA) and aortic (Ao) pressure and systemic flow (Qs) tracings from a lamb treated with phenoxybenzamine before left pulmonary artery balloon distention. Incomplete blockade is present with persistent aortic pressure changes.

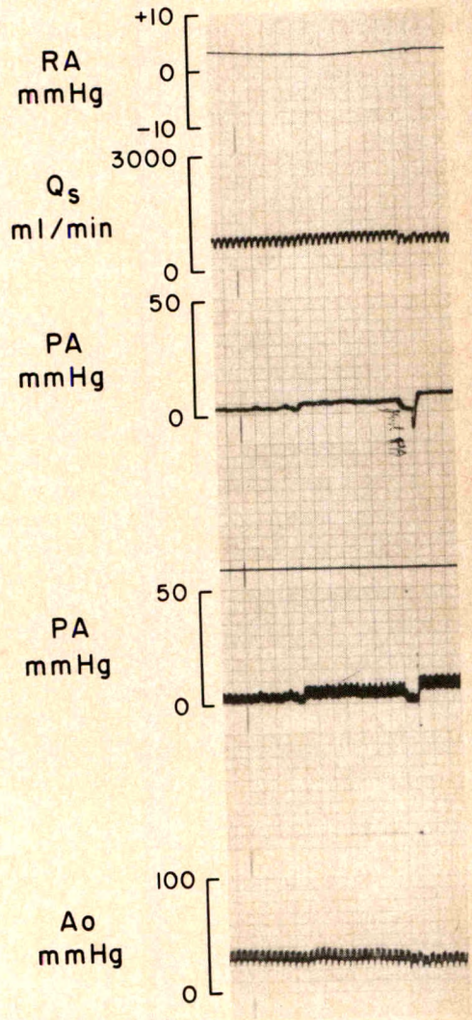

FIGURE 4. Right atrial (RA), pulmonary artery (PA) and aortic (Ao) pressure and systemic flow (Qs) tracings from the same lamb as in Figure 3. The distal pulmonary artery and aortic pressure changes are obliterated after administration of an additional dose of phenoxybenzamine. In addition, substantial vasodilation has developed, accounting for the decreases in aortic and pulmonary artery pressures.

aortic pressure was observed in response to balloon distention in the main PA, yet the calculated SVR did not change.[3] However, diastolic aortic pressure, which correlates with SVR,[13,14] increased significantly, suggesting that changes in SVR escaped detection. Finally, unanesthetized sheep, including newborns, 3-month-old lambs and adult sheep have been evaluated during balloon distention of the proximal main PA. The adult sheep had small but significant increases in aortic pressure, whereas the newborns did not.[2] The investigators implied that SVR did not change, yet the cardiac output decreased significantly. Consequently, SVR must have increased in order to maintain the elevated or constant aortic pressure observed.

The variable findings just described may be a result of biologic variability or of effects of anesthesia. Alpha chloralose was used as the anesthetic in our studies because it has been shown to have less severe depressant effects on ventricular performance and greater preservation of reflex activity, particularly baroreceptor reflexes, in some species.[15,16] Whether the increase in SVR would be enhanced using an unanesthetized preparation remains to be determined.

Our finding that acute PA distention causes increases in pulmonary arterial pressure is similar to observations by other investigators.[1–3] The pulmonary effects have not been abolished by vagotomy,[17] but can be blocked with lidocaine infiltration of the main PA, by the infusion of 6-hydroxydopamine, which causes selective destruction of adrenergic nerve terminals and depletion of norepinephrine, or by surgical denervation of the pulmonary artery. Apparently, the pulmonary vasoconstrictive mechanism primarily involves the release of norepinephrine at nerve endings.[17] Our findings of blocked PA pressure changes in limited trials with α-adrenergic blockade are also consistent.

The pulmonary vasoconstrictive mechanism may have several roles. In the fetus, hypoxemia enhances pulmonary vasoconstriction. This, in turn, may lead to distention of proximal segments of the PA, which results in further pulmonary vasoconstriction, preferentially shunting blood across the ductus arteriosus to the placenta. After birth, as the pulmonary vascular resistance decreases with lung expansion and improved oxygenation, PA distention may diminish, resulting in still further increases in pulmonary blood flow.

The role of the autonomic nervous system in systemic vascular changes has also been studied in adult animals. Systemic effects can be blocked with vagotomy,[4] as well as local infiltration of the main PA with phentolamine or 2% lidocaine.[5] Our results with limited trials using autonomic blocking agents and vagotomy are similar to those of others.[4,5,17] However, we cannot conclude whether the proposed norepinephrine release into the circulation is more critical than autonomic nervous control in the changes observed.

Some interdependence appears to exist between the systemic and pulmonary vascular beds, which can be triggered in newborn lambs by distention of the pulmonary artery distal to its bifurcation. Although the physiologic role of the systemic vasoconstrictor response is unclear, it could be important in the redistribution of cardiac output observed in the hypoxemic fetus.

Acknowledgment: We gratefully acknowledge Stephen H. Bennett for technical assistance.

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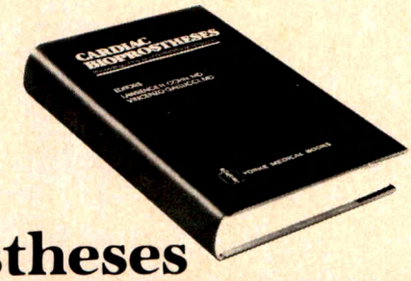

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Proceedings of the Second International Symposium
Rome, Italy, May 17-19, 1982

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
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Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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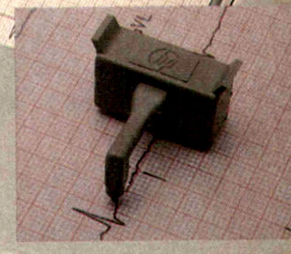

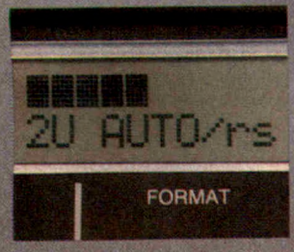

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Brief Summary
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INDICATIONS: MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.
WARNINGS: Minipress may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120–160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution. (See DOSAGE AND ADMINISTRATION.) Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsule of MINIPRESS. The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure; namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS in pregnancy has not been established. MINIPRESS is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS some of them rarely. (In some instances exact causal relationships have not been established.)

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus, alopecia, lichen planus.

Genitourinary: urinary frequency, incontinence, impotence, priapism.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See WARNINGS.)

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

OVERDOSAGE: Accidental ingestion of at least 50 mg of MINIPRESS in a two year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.

Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate MINIPRESS is not dialysable because it is protein bound.

TOXICOLOGY: Testicular changes, necrosis and atrophy have occurred at 25 mg/kg/day (60 times the usual maximum recommended dose of 20 mg per day in humans) in long term (one year or more) studies in rats and dogs. No testicular changes were seen in rats or dogs at the 10 mg/kg/day level (24 times the usual maximum recommended dose of 20 mg per day in humans). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS (prazosin hydrochloride) therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on MINIPRESS (prazosin hydrochloride) alone for up to 51 months did not demonstrate changes in sperm morphology suggestive of drug effect.

HOW SUPPLIED: MINIPRESS is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

References: 1. Pitts NE: The clinical evaluation of prazosin, a new antihypertensive agent, in Prazosin Clinical Symposium Proceedings. Published as a special report by *Postgraduate Medicine*. New York, McGraw-Hill Book and Education Services Group, 1975, pp 117-127. **2.** Adapted from Kaplan NM: Summary: *J Cardiovasc Pharmacol* 4 (suppl 2): S265, 1982. **3.** Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in Prazosin Clinical Symposium Proceedings. Published as a special report by *Postgraduate Medicine*. New York, McGraw-Hill Book and Education Services Group, 1975, pp 45-52.

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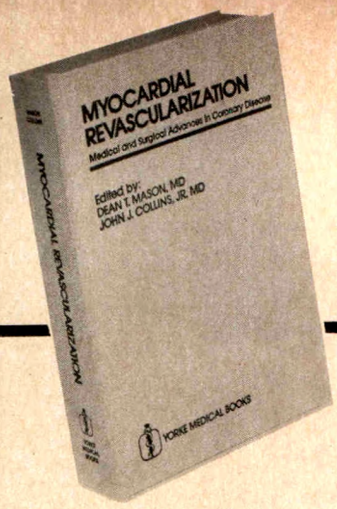

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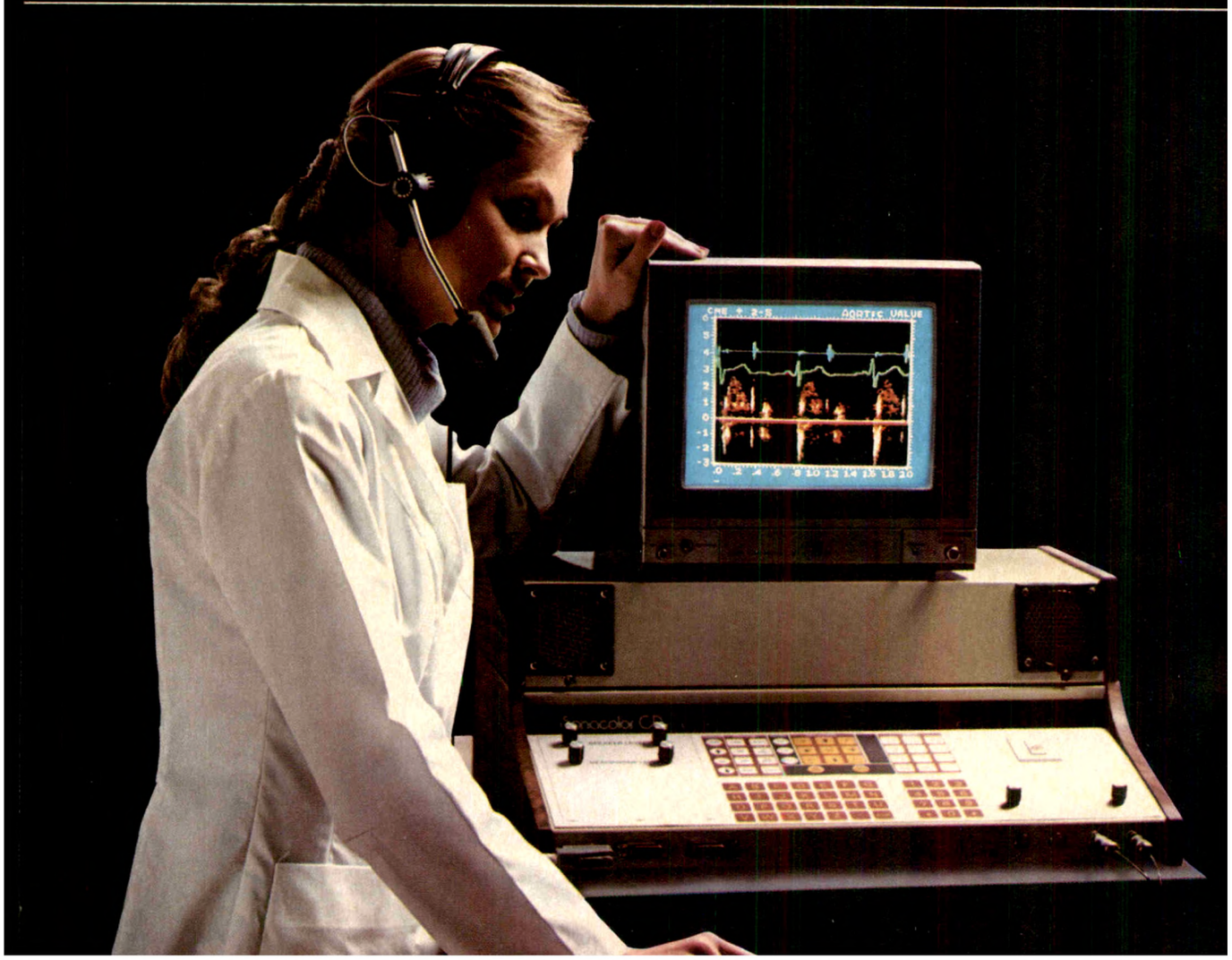

Pharmacokinetics and Pharmacodynamics of Milrinone in Chronic Congestive Heart Failure

JOSEPH R. BENOTTI, MD, LAWRENCE J. LESKO, PhD, JANE E. McCUE, RN, and JOSEPH S. ALPERT, MD

The acute hemodynamic effects and pharmacokinetics of bolus intravenous milrinone administration were assessed in 13 patients with severe congestive heart failure. Serial hemodynamics were measured and blood samples were obtained to determine plasma milrinone concentration and calculation of pharmacokinetic variables after administration of milrinone at 12.5, 25, 50 and 75 μg/kg, allowing at least 6 hours to elapse between consecutive milrinone doses. At each dose milrinone effected prompt but very short-lived increases in cardiac output and left ventricular stroke work and decreases in pulmonary artery pressure, right atrial pressure and systemic and pulmonary vascular resistance in a non-dose-dependent fashion. Pulmonary artery wedge pressure decreased in a dose-related manner. Heart rate increased significantly after the 75-μg/kg dose and mean arterial pressure decreased significantly only after the 50- and 75-μg/kg milrinone dose. The time-dependent decline in plasma milrinone concentration was biexponential and log linear, conforming to an open 2-compartment model of drug distribution and elimination. Mean plasma milrinone clearance (± standard error) was 0.15 ± 0.03 liters/min/kg, volume of distribution was 0.35 ± 0.02 liters/kg and mean elimination half-life was 1.7 hours.

(Am J Cardiol 1985;56:685–689)

Milrinone, a bipyridine derivative, is one of several recently developed nonglycoside, nonsympathetically mediated, positive inotropic agents. Milrinone exerts a positive inotropic effect in vitro as evidenced by an increase in myocardial force generation, an increase in ventricular developed tension and the peak rate of isovolumic ventricular pressure generation (LV dP/dt) in isolated myocardial tissue, isolated heart preparations and laboratory animals.[1–3] Exploratory efficacy studies in patients with advanced congestive heart failure (CHF) show that milrinone administered intravenously and orally improves cardiac index, lowers pulmonary artery wedge and right atrial pressures and dramatically lowers systemic vascular resistance[4,5] while increasing the peak rate of LV dP/dt.[4] Its salutary hemodynamic effects are probably exerted, in part, through an inotropic and vasodilator mechanism of action. Some additional benefit may accrue from the ability of milrinone to improve diastolic ventricular compliance.[6] This study was designed to elucidate the pharmacokinetics and pharmacodynamics of milrinone administered intravenously on an incremental bolus dose schedule.

From the Division of Cardiovascular Medicine, University of Massachusetts Medical Center, Worcester, Massachusetts, and the Pharmacokinetics Laboratory, University of Maryland School of Pharmacy, Baltimore, Maryland. This investigation was supported in part by a grant from the Sterling Winthrop Research Institute, Rensselaer, New York. Manuscript received March 4, 1985; revised manuscript received May 3, 1985, accepted May 13, 1985.

Address for reprints: Joseph Benotti, MD, Division of Cardiovascular Medicine, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, Massachusetts 01605.

Methods

According to a protocol approved by the Committee on the Protection of Human Subjects in Research at the University of Massachusetts Medical Center, all consecutive patients with New York Heart Association class III or IV symptoms of CHF and an ejection fraction of less than 0.40 while receiving digoxin and diuretic therapy were candidates for this investigation. Patients were excluded from participation in this protocol if they had (1) myocardial infarction within the preceding 3 months, (2) limitation of exercise capacity by angina rather than by dyspnea or fatigue, (3) untreated sustained ventricular tachycardia, (4) serious primary hepatic or renal dysfunction (serum creatinine 3.0 mg/dl or more), (5) cardiac index greater than 2.5 liters/min/m^2, and (6) pulmonary artery wedge pressure less than 15 mm Hg.

Each patient was maintained on a no-added-salt diet and a stable dose of digoxin and diuretics. Twenty-four hours before milrinone administration, all vasodilator treatment was discontinued. The patient was transferred to the coronary care unit, where a triple-lumen thermodilution Swan-Ganz catheter was advanced into the pulmonary artery. After baseline hemodynamic stability was established (less than 10% variation in cardiac output and pressures on at least 2 consecutive measurements at least 1 hour apart), intravenous milrinone was administered as a 12.5-μg/kg dose at 100 μg/s. Serial hemodynamic measurements and 5-ml blood specimens were obtained to determine plasma milrinone concentration at 5, 10, 15, 30, 60, 180 and 360 minutes after each dose. Six hours after the first dose each patient received milrinone as 25 μg/kg by intravenous bolus at 100 μg/s with serial hemodynamic measurements and blood sampling as previously outlined. After a night of rest the patient received his or her third milrinone dose (50 μg/kg) 24 hours after the 12.5-μg/kg milrinone dose, with serial hemodynamic measurements and blood

TABLE I Hemodynamic Response to Milrinone (n = 13)

Milrinone Dose (μg/kg)	CO (liters/min)	PAW (mm Hg)	LVSW (g-m)	MAP (mm Hg)	PAP (mm Hg)	RAP (mm Hg)	SVR (Wood units)	PVR Wood units	HR (beats/min)	Peak Plasma Milrinone (ng/ml)
C_1	4.5 ± 1.1	21 ± 7	70.3 ± 25.4	84 ± 9	31 ± 8	11 ± 10	16.7 ± 4.1	2.3 ± 0.9	83 ± 9	
12.5	6.0 ± 1.4*	17 ± 8*	99.5 ± 29.8*	84 ± 10	26 ± 11*	9 ± 8*	13.3 ± 4.3*	1.6 ± 1.2*	83 ± 12	81 ± 40
C_2	4.4 ± 0.9	19 ± 8	68.1 ± 20.8	82 ± 11	30 ± 12	11 ± 9	16.7 ± 4.1	2.6 ± 1.3	89 ± 18	
25.0	6.0 ± 1.3*	17 ± 8	91.3 ± 22.4*	85 ± 8	27 ± 11*	8 ± 9*	13.4 ± 4.4*	1.5 ± 1.3*	92 ± 15	169 ± 32
C_3	4.2 ± 1.0	20 ± 6	64.8 ± 25.2	85 ± 9	31 ± 9	10 ± 8	18.3 ± 4.0	2.8 ± 1.6	85 ± 10	
50.0	6.1 ± 1.4*	13 ± 8†	91.7 ± 26.0*	80 ± 11*	24 ± 11*	6 ± 7*	12.3 ± 3.2*	1.8 ± 1.1*	88 ± 14	272 ± 50
C_4	4.5 ± 1.3	21 ± 7	69.3 ± 19.2	83 ± 9	32 ± 9	13 ± 8	16.3 ± 3.3	2.5 ± 1.9	84 ± 13	
75.0	6.6 ± 1.7*	11 ± 8†	99.9 ± 33.2*	79 ± 7*	25 ± 9*	8 ± 10*	11.2 ± 3.4*	2.0 ± 1.3*	93 ± 14*	454 ± 55

* $p < 0.05$ relative to control; † $p < 0.05$ relative to peak response after the 12.5- and 25-μg/kg doses.
C_1–C_4 = control hemodynamic parameters (as defined in text); CO = cardiac output; HR = heart rate; LVSW = left ventricular stroke work; MAP = mean arterial pressure; PAP = pulmonary artery pressure; PAW = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SVR = systemic vascular resistance.

sampling for milrinone concentrations obtained as above. The fourth dose, 75 μg/kg was then administered 6 hours after the third dose, again with serial hemodynamic monitoring and milrinone plasma level determinations.

Cardiac output was measured in triplicate by the thermodilution technique. Mean arterial pressure was measured as the electrical integral of the phasic oscilloscopic signal or as the sum of diastolic pressure plus one-third pulse pressure when measured by sphygmomanometer. For all pressures the 0 reference point was taken at 5 cm below the sternal angle. Derived hemodynamic variables were calculated according to standard formulas.[7]

Blood for plasma milrinone concentration determination was collected in citrated tubes, immediately centrifuged and the supernatant (plasma) was frozen at −60°C. Milrinone plasma levels were determined by a high-performance gas liquid chromatography technique.[8] Those analyzing and reporting milrinone plasma levels were not intentionally blinded to milrinone dose, time after dose or hemodynamic responses.

An open 2-compartment model was fitted simultaneously to the plasma milrinone concentration-time data obtained after each successive milrinone dose by nonlinear regression analysis using ADAPT.[9] Model-dependent kinetic parameter values of total body clearance (CL), volume of distribution (V_z) and elimination rate constant (λ_z) were calculated from regression-dependent micro rate constants and volume terms as follows[10]: $CL = k_{10}V_c$; $V_z = CL/\lambda_z$; $\lambda_z = 1/2[(k_{12} + k_{21} + k_{10})] - [(k_{12} + k_{21} + k_{10})^2 - 4k_{21}k_{10}]^{1/2}$.

The terminal elimination half-life ($t_{1/2}$) was calculated as: $t_{1/2} = \ln 2/\lambda_z$.

For each patient at each milrinone dose, hemodynamic variables were measured at the time of the maximal cardiac output. Baseline hemodynamic variables are average values of 2 sets of data recorded one-half hour before and just before drug administration. Comparisons between peak response relative to baseline for each milrinone dose, between consecutive baselines and between peak hemodynamic responses after each milrinone dose were made using an analysis of variance.

Results

Our study population was composed of 10 men and 3 women, aged 43 to 81 years. Eleven had New York Heart Association class IV symptoms and 2 had class III symptoms. CHF resulted from advanced coronary heart disease in 11 patients and from nonischemic dilated cardiomyopathy in 2. The hemodynamic action and kinetic behavior of milrinone in these 2 patients was indistinguishable from those of the 11 patients with coronary heart disease. No patient had responded satisfactorally to digoxin, diuretics and vasodilators in optimal doses. The advanced state of LV dysfunction in each patient was evidenced by a severe depression in LV ejection fraction, ranging from 0.08 to 0.27.

Table I describes the group mean peak hemodynamic responses to the 4 consecutive milrinone doses and the group mean maximal plasma milrinone concentration after consecutive milrinone doses. Cardiac output increased significantly with each dose, to 6.0, 6.0, 6.1 and 6.6 liters/min after the 12.5- 25-, 50- and 75-μg/kg milrinone doses, respectively. Analysis of variance revealed no significant differences between maximal cardiac output after each dose. Pulmonary artery wedge pressure decreased significantly to 17, 13 and 11 mm Hg after milrinone administration at 12.5, 50 and 75 μg/kg,

respectively. The overall tendency was that the percent decrease in wedge pressure increased; 19%, 11%, 35% and 48% after the 12.5-, 25-, 50- and 75-μg/kg milrinone doses. The wedge pressure reduction after the 50- and 75-μg/kg doses significantly exceeded that after the 12.5- and 25-μg/kg milrinone doses, consistent with a dose-response relation. After each dose, milrinone significantly increased LV stroke work in a non-dose-related fashion. Mean arterial pressure decreased slightly but significantly only after the 50- and 75-μg/kg doses. Mean pulmonary artery pressure decreased significantly, from the 30- to 32-mm Hg range, during the control period to 26, 27, 24 and 25 mm Hg, respectively, as the milrinone dosage was increased. No dose-response relation was discernible. Right atrial pressure decreased significantly after milrinone administration, from the 10 to 13 mm during the control period to 9, 8, 6 and 8 mm Hg as the milrinone dosage was increased, with no demonstrable dose-response relation. Systemic vascular resistance decreased significantly, to 13.3, 13.4, 12.3 and 11.2 Wood units after each milrinone dose. The decrease in systemic vascular resistance was dose-independent, as there was no significant difference between systemic vascular resistance values measured after successively larger milrinone doses. Pulmonary vascular resistance, initially slightly elevated, decreased significantly with milrinone administration. No dose-response relation was discernible. Heart rate increased significantly only after the largest milrinone dose.

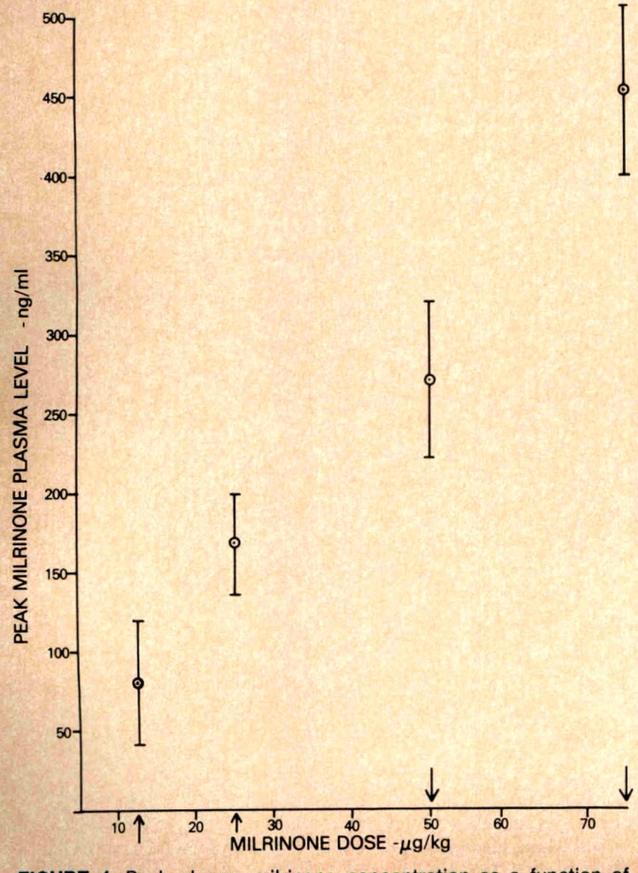

FIGURE 1. Peak plasma milrinone concentration as a function of dose.

The peak hemodynamic response to milrinone occurred at or within 60 minutes of dosing. Hemodynamic measurements returned to baseline values by 90 minutes after drug administration.

Peak plasma milrinone concentration rose linearly with dosage (Fig. 1). No correlation was found between the maximal cardiac output and plasma milrinone concentration (Fig. 2).

Figure 3 is a ventricular function curve in which cardiac output was plotted against pulmonary artery wedge pressure. Because no significant differences were found between the control cardiac output values and pulmonary wedge pressure values preceding each milrinone dose, they were averaged and are represented by point C. $M_{1,2}$ represents mean cardiac output and pul-

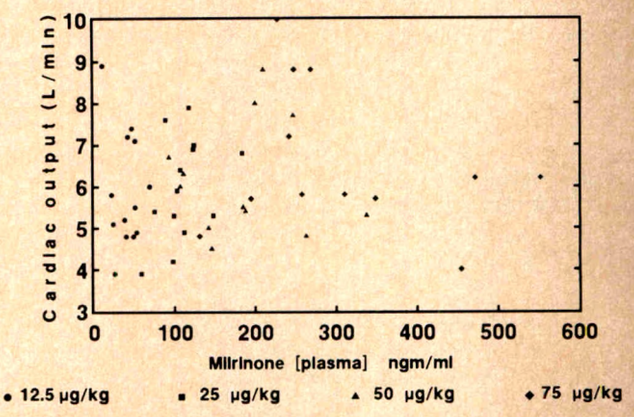

FIGURE 2. Relation between individual maximal cardiac output after each milrinone dose and simultaneous plasma milrinone concentration.

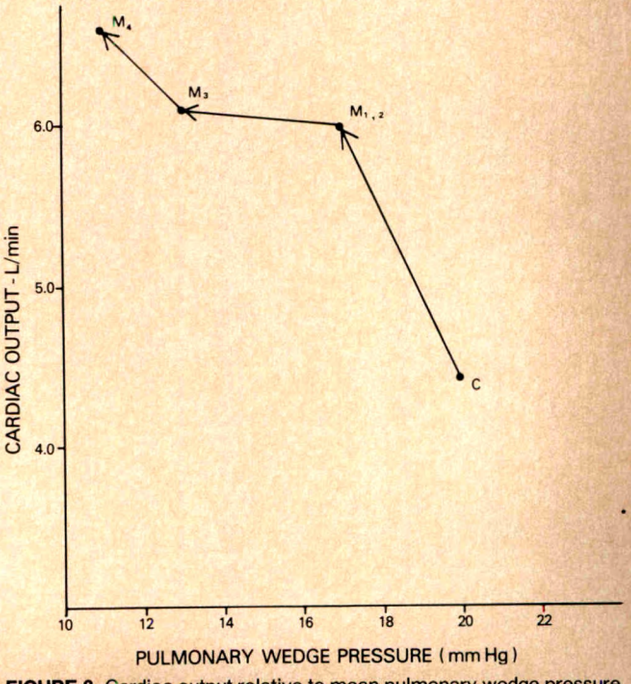

FIGURE 3. Cardiac output relative to mean pulmonary wedge pressure expressed as a function of increasing milrinone dose. See text for details.

monary wedge pressure after milrinone doses of 12.5 and 25 μg/kg and M_3 and M_4 represent cardiac output and pulmonary wedge pressure after doses of 50 and 75 μg/kg. Although the increase in cardiac output plateaus as the milrinone dose increases (Table I) and the individual maximal cardiac output appears to be independent of simultaneous plasma milrinone concentration (Fig. 2), overall ventricular performance (expressed as cardiac output as a function of pulmonary artery wedge pressure) improves as the milrinone dose increases.

Figure 4 shows observed and predicted plasma milrinone concentrations obtained by simultaneous modeling in a representative patient. It shows the close correlation between observed and calculated plasma milrinone concentrations. Plasma milrinone concentration declines biexponentially with time after milrinone injection. The biexponential equation describing the time course of milrinone plasma concentrations preceding the lowest milrinone dose is also shown. A 2-compartment body model adequately described the disposition of milrinone in each patient.

The derived kinetic parameter values for milrinone include a mean CL of 0.15 liters/kg/hour (range 0.11 to 0.20) and a mean V_z of 0.35 liters/kg (range 0.24 to 0.44). The milrinone half-life values ranged from 1.3 to 2.2 hours (mean ± standard deviation 1.7 ± 0.3).

Discussion

This investigation demonstrates that milrinone in incremental intravenous doses up to 75 μg/kg elicits significant but very abbreviated improvements in ventricular function. These are manifested by increases in cardiac output and LV stroke work and decreases in pulmonary artery wedge and right atrial pressure. Systemic vascular resistance decreases significantly, heart rate increases significantly and blood pressure decreases only with the highest milrinone dose. The salutary hemodynamic changes are compatible with an inotropic and vasodilator mechanism of action. Baim et al[4] and Collucci et al[13] published preliminary data that suggests that milrinone exerts its beneficial hemodynamic effect, at least in part, by a positive inotropic action. In vitro and experimental animal data also suggest that milrinone has an inotropic mechanism of action.[1–3]

The explanation for the pleateau relation between milrinone dose and hemodynamic response is not clear. As ventricular function improves with milrinone, a drug that exerts its beneficial effects through a nonglycoside, noncatecholamine-mediated mechanism of action,[1–3] evoked hemodynamic changes may work in concert to attenuate further functional improvement despite further dosage increases. Cardiac preload may be reduced as a result of reflex withdrawal of venular tone or overall hemodynamic improvement, or owing to a direct dilatory effect of milrinone on venous smooth muscle. In this manner, milrinone may redistribute blood away from the central circulation, thereby reducing LV end-diastolic volume. This would limit the maximal increase in cardiac output attainable. Indeed, our data suggest that higher doses of milrinone (50 and 75 μg/kg) reduced pulmonary artery wedge pressure to

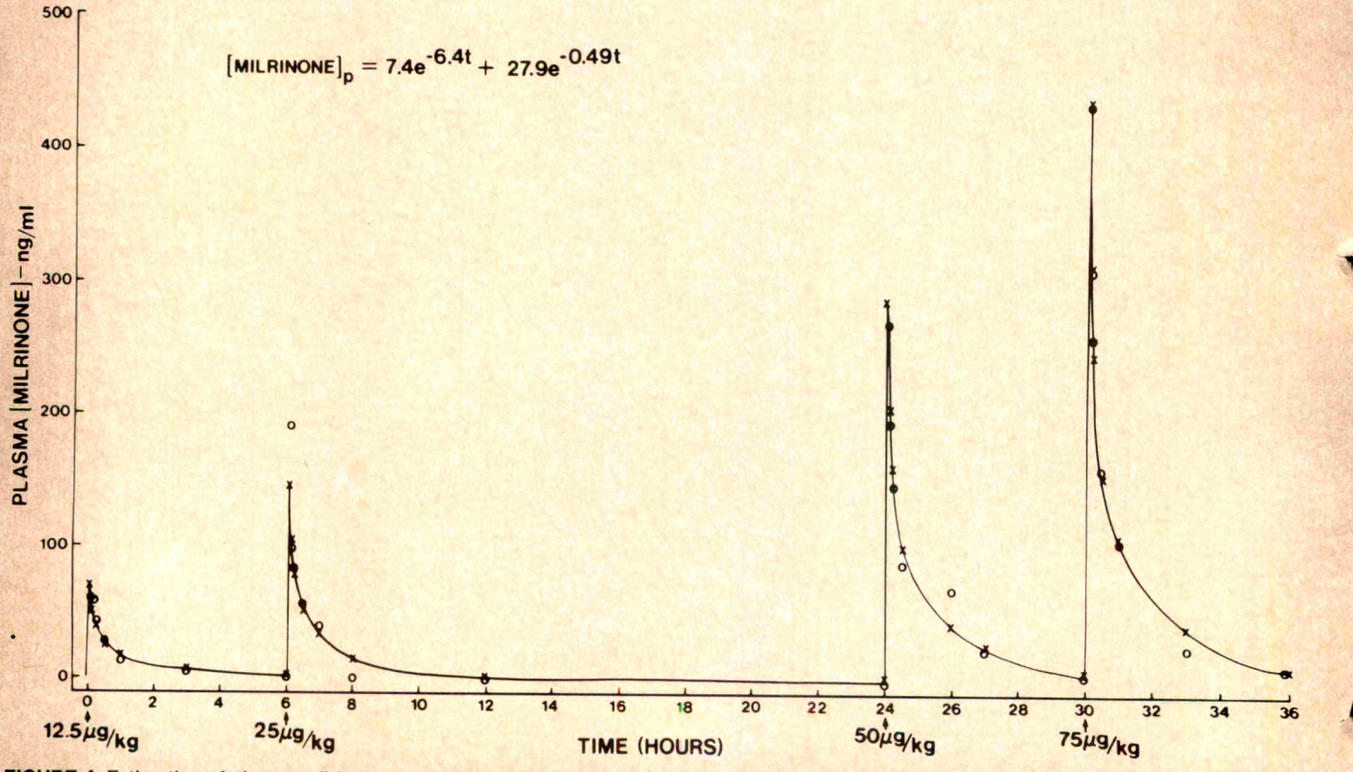

FIGURE 4. Estimation of plasma milrinone concentration for repetitive doses in a representative patient using the "Adapt" program for multiple dosing. Close agreement between the computer-derived curve (drawn from estimated milrinone plasma levels [x]) with the measured milrinone plasma levels (**open circles**) is apparent.

a greater degree than lower milrinone doses (12.5 and 25 μg/kg). As the wedge pressure declines below 15 mm Hg in most patients with CHF, it is likely that any further decline in preload would limit subsequent increase in cardiac output effected by further improvements in the inotropic state of the myocardium or decreases in afterload effected by a larger milrinone dose. The plateau relation between milrinone dose and hemodynamic response may also be explained by milrinone's presumed mechanism of action as a phosphodiesterase inhibitor. Doses of milrinone in excess of that required for maximal phosphodiesterase inhibition should effect little, if any, additional hemodynamic improvement. These data suggest that there is a plateau in the response to bolus milrinone administration in doses in excess of 50 to 75 μg/kg/min. Higher doses may cause an undesirable increase in heart rate or decline in mean arterial pressure without further improving cardiac output.

The characterization of milrinone disposition by a 2-compartment open model after repeated intravenous bolus administration is in agreement with the observations of Stroshane et al.[11,12] They reported a similar disposition profile in patients with CHF and in normal volunteers. Their CL (0.11 ± 0.01 liters/kg/hour) in patients with CHF was similar to the mean CL (0.15 liters/kg/hour) found in this study. The volumes of distribution in CHF were very similar (0.33 vs 0.35 liters/kg). Because of almost identical CL and V_z parameter values in each study, the terminal elimination half-life values in their study (1.8 hours) and our study (1.7 hours) were identical. By contrast, they found that the elimination half-life of milrinone in normal volunteers was markedly less, 0.8 hours, primarily owing to a faster CL (90.28 liters/kg/hour) and not because of a smaller distribution volume. A major question that must be addressed is whether plasma clearance of milrinone increases and its elimination half-life shortens as cardiac function improves.

Relative to dopamine or dobutamine, milrinone has a longer elimination half-life. Accordingly, a loading bolus followed by a continous intravenous infusion is required to achieve a prompt, therapeutically effective steady-state plasma level. However, the elimination half-life of milrinone (1.7 to 1.8 hours) is short enough that the plasma concentration should promptly decrease following discontinuation of intravenous infusion. Accordingly, any potentially undesirable hemodynamic effects should resolve reasonably promptly with dose reduction or drug discontinuation.

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Effects of Hydralazine on Pressure-Volume and Stress-Volume Relations in Congestive Heart Failure Secondary to Idiopathic Dilated Cardiomyopathy

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The mechanism by which hydralazine improves cardiac function in patients with heart failure is not well characterized. Hydralazine may improve left ventricular (LV) function by decreasing afterloading wall stress or by increasing myocardial contractility. The effect of intravenous hydralazine was assessed in 8 patients with severe idiopathic dilated cardiomyopathy. Hydralazine increased stroke volume index (from 24 ± 8 to 40 ± 9 ml/m², p <0.01) and decreased systemic vascular resistance (from 1,603 ± 619 to 810 ± 317 dynes s cm^{-5}, p <0.01) and peak LV wall stress (from 476 ± 118 to 410 ± 68 kdynes/cm², p = 0.02). Two groups were defined by normal or high LV wall stress. Patients with high LV stress had higher LV end-diastolic pressure (38 ± 12 vs 17 ± 8 mm Hg, p <0.01), LV end-diastolic volume index (184 ± 24 vs 149 ±7 ml/m², p <0.01) and systemic vascular resistance (1,423 ± 686 vs 846 ± 293 dynes s cm^{-5}, p = 0.01). Hydralazine decreased stress more in these patients (−101 ± 57 vs −6 ± 9 kdynes/cm², p = 0.02), LV end-diastolic pressure (−12 ± 7 vs 2 ± 2 mm Hg, p = 0.02), systolic pressure (−15 ± 13 vs 3 ± 4 mm Hg, p = 0.03) and systemic vascular resistance (−1,053 ± 247 vs −363 ± 83 dynes s cm^{-5}, p <0.01) than in patients with normal LV stress. Decreased LV stress was caused by decreased systolic and diastolic pressures and/or volumes. Late systolic pressure-volume relations in patients with normal LV stress suggested increased myocardial contractility, but this was not confirmed by LV dP/dt. Hydralazine improves LV function in patients with dilated cardiomyopathy by reducing elevated LV wall stress, with little inotropic effect.

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Although hydralazine administration increases stroke volume in patients with chronic congestive heart failure, the mechanism of this response is not well established. Patients differ in responsiveness to vasodilators, which has been related to differences in systemic vascular resistance, left ventricular end-diastolic pressure (LVEDP), and LV cavity size.[1,2] The association of LV dilation with a good response to hydralazine suggests that vasodilators may act through a reduction in LV wall stress.[2–6] The positive inotropic effect of hydralazine may also play a role.[7] To assess the role of LV stress and inotropy in hydralazine therapy, we examined the effect of intravenous hydralazine on LV pressure-volume and stress-volume relations, vascular resistance, and indexes of cardiac performance in 9 patients with idiopathic dilated cardiomyopathy.

From the Division of Cardiology, University of Texas Health Science Center, the Cardiology Service, Veterans Administration Medical Center, Dallas, Texas, and the Cardiology Division, University of Virginia Medical Center, Charlottesville, Virginia. This study was supported in part by Training Grant HLO-7360 from the National Institutes of Health, Bethesda, Maryland, and by a grant from the Virginia Affiliate of the American Heart Association, Richmond, Virginia. Manuscript received February 18, 1985; revised manuscript received April 29, 1985, accepted April 30, 1985.

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Methods

Patients: Nine patients were studied during cardiac catheterization after optimal diuresis without vasodilator therapy, often requiring both furosemide (as much as 800 mg/day) and metolazone (as much as 10 mg/day). No complications resulted from this study.

Hydralazine administration: Hydralazine was administered intravenously in sequential 5-mg doses every 5 minutes, titrated to decrease arteriovenous oxygen saturation difference to about half baseline values, approximately doubling cardiac output. The mean total dose was 27 mg (range 10 to 60).

Catheterization: Biplane left ventriculography with simultaneous LV micromanometry (Millar Instruments), dP/dt and right atrial pressure recordings were performed before and after hydralazine administration. Central aortic micromanometer pressure was recorded immediately before each ventriculogram. Contrast-induced pressure shifts during ventriculography[8,9] were avoided either by using 2 catheters or by using a custom-guiding catheter that allowed intraventricular micromanometer placement during injection. At least 30 minutes elapsed between ventriculograms taken before and after administration of hydralazine to allow contrast effects to dissipate.[8,9] Coronary arteriography showed no significant coronary artery disease.

Data calculation: Biplane LV images were digitized frame by frame (60 frames/s) over 2 successive cardiac cycles both before and after hydralazine administration. LV perimeters were corrected for pincushion distortion and tube-to-screen magnification by a biplane triangulation technique.[10] LV volume was calculated by the biplane area-length method.[11]

TABLE I Clinical and Hemodynamic Characteristics of Patients in Order of Decreasing Peak Left Ventricular (LV) Stress

Pt	Age (yr)	Duration of CHF (mo)	C/H	HR (beats/ min)	LV Stress Peak (kdynes/cm²)	LV Stress Mean Systolic (kdynes/cm²)	LVP S/EDP (mm Hg)	ArtP S/D (mm Hg)	EDVI (ml/m²)	SVI (ml/m²)	EF (%)	Peak dP/dt (mm Hg/s)	SVR (dynes s cm⁻⁵)
High Stress													
1	62	1	C	72	621	506	133/34	133/85	168	23	14	1,025	1,646
			H	73	471	333	107/21	107/58	180	49	27	897	824
2	65	11	C	104	599	474	141/48	141/97	238	20	8	934	1,838
			H	106	456	371	119/27	119/72	212	37	17	794	709
3	42	36	C	90	536	470	116/55	116/86	189	21	11	—	2,784
			H	83	496	396	115/51	115/85	183	46	25	—	1,524
4	49	42	C	84	532	500	115/47	115/90	168	17	10	580	1,905
			H	74	397	283	88/30	88/61	168	34	20	486	613
5	49	23	C	112	479	305	89/34	89/67	169	18	11	890	1,574
			H	115	440	195	88/29	88/64	165	26	16	904	811
Normal Stress													
6	58	14	C	105	379	309	112/6	112/47	141	21	15	1,011	1,341
			H	108	376	318	118/9	118/54	139	28	20	1,059	899
7	64	12	C	99	374	301	103/17	103/70	153	25	16	828	894
			H	100	357	247	101/19	101/65	153	44	29	787	525
8	53	1	C	99	289	195	88/26	85/55	153	43	28	690	848
			H	82	290	207	93/26	93/63	154	54	35	620	571
Mean ± Standard Deviation													
	55 ± 8	18 ± 15	C	96 ± 13	476 ± 118	383 ± 118	112 ± 19/ 33 ± 17	112 ± 19/ 75 ± 17	172 ± 30	24 ± 8	14 ± 6	851 ± 165	1,603 ± 619
			H	93 ± 17	410 ± 68†	294 ± 74*	104 ± 13/ 27 ± 12	104 ± 13/ 65 ± 10	170 ± 23	40 ± 9*	24 ± 6*	733 ± 214	810 ± 317*
High stress (Pts 1–5)	53 ± 9	23 ± 15		91 ± 17	503 ± 70	383 ± 105	111 ± 18/ 38 ± 12	111 ± 18/ 77 ± 14	184 ± 24	30 ± 12	16 ± 7	761 ± 214	1,423 ± 686
Normal stress (Pts 6–8)	58 ± 9	9 ± 6		99 ± 9	344 ± 43*	262 ± 54*	103 ± 11/ 17 ± 8*	103 ± 11/ 60 ± 8*	149 ± 7*	36 ± 13	24 ± 8*	832 ± 174	846 ± 293*
Change—Control to Hydralazine													
High stress (Pts 1–5)				−2 ± 6	−101 ± 57	−135 ± 58	−15 ± 13/ −12 ± 7	−15 ± 13/ −17 ± 14	−4 ± 14	20 ± 5	11 ± 2	−192 ± 143	−1,053 ± 247
Normal stress (Pts 6–8)				−4 ± 11	−6 ± 9†	−11 ± 37*	3 ± 4†/ 2 ± 2†	3 ± 4†/ 3 ± 6†	0 ± 2	12 ± 6	8 ± 4	−21 ± 61	−363 ± 83*

* $p \leq 0.01$; † $p < 0.05$ vs control or vs high stress group, defined by analysis of variance.
ArtP = arterial pressure (systemic); C = control; CHF = congestive heart failure; D = diastolic; EDP = end-diastolic pressure; EDVI = end-diastolic volume index; EF = ejection fraction; H = hydralazine; HR = heart rate; LVP = left ventricular pressure; S = systolic; SVI = stroke volume index; SVR = systemic vascular resistance.

LV mass was calculated from radiographic end-diastolic wall thickness.[12] Wall thickness was calculated for each frame by an iteration technique using the first mass.[13] Circumferential wall stress was calculated from the formula for a thin-walled prolate spheroid.[14] LV wall stress and systemic vascular resistance were considered high when they exceeded 450 kdynes/cm^2 and 1,500 dyne s cm^{-5}, respectively.[15,16]

Central aortic pressure was superimposed on LV pressure to determine the time of aortic valve closure, which was used to determine end-systolic pressure and wall stress. The smallest LV volume determined end-systolic volume. Peak dP/dt was taken from the analog derivative of the pressure tracing.[17]

Statistical methods: Ventriculographic data were smoothed using a 9-point polynomial approximation technique. Values presented are the average of the 2 consecutive beats. The significance of differences was defined by analysis of variance.

Accuracy and reproducibility: Immediately before each ventriculogram, micromanometer pressure traces were superimposed on simultaneous LV pressure traces from mercury-calibrated air-reference transducers. The accuracy of pressures is therefore within 5 mm Hg. Our computerized x-ray dimension system[10] can measure distances between beads randomly oriented in the x-ray field with 95% confidence limits (±2 standard deviations) of ±1 mm, and can measure the volume of human LV latex casts with 95% confidence limits of ±15 ml, which is less than 5% of most LV volumes in these patients.

Results

Table I is a summary of clinical characteristics and hemodynamic values in the 8 patients during control conditions and after hydralazine administration. Patients 1 to 8 are arranged in order of decreasing peak LV

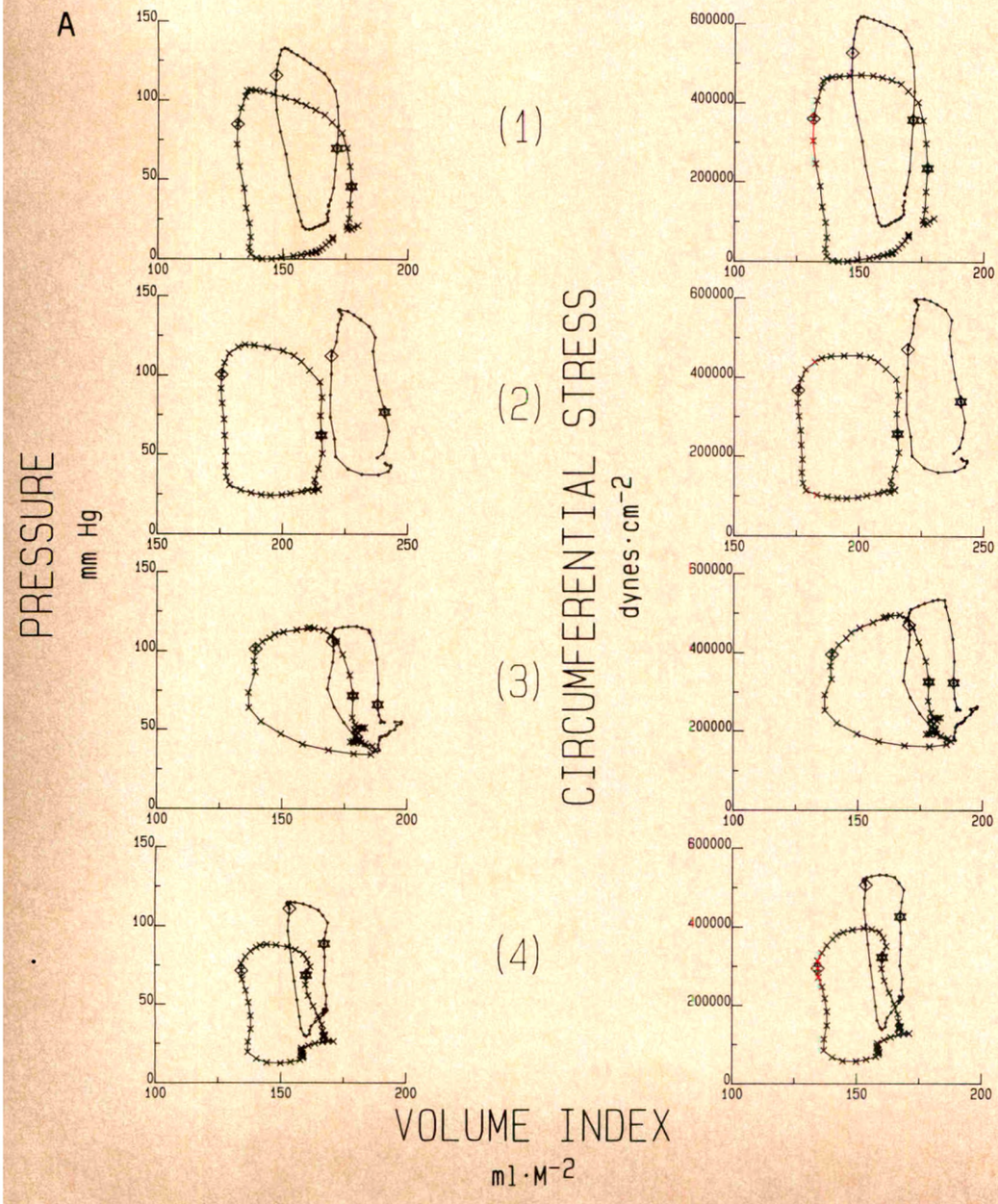


FIGURE 1. A and **B**, pressure-volume (**left**) and stress-volume (**right**) loops in patients before (**dots**) and after (**x**) hydralazine infusion. **Stars** mark aortic valve opening and **diamonds** mark aortic valve closure. Patient 2's value is plotted on a larger volume axis than the others. In patients 1 (**A**) to 5 (**B** on opposite page), who have higher pretreatment wall stress and greater ventricular dilation, hydralazine caused prominent diastolic effects not seen in patients with lower pretreatment wall stress and less ventricular dilation (nos. 6 to 8, opposite page). In the latter patients, end-systolic volume decreased whether or not end-systolic pressure and stress decreased.

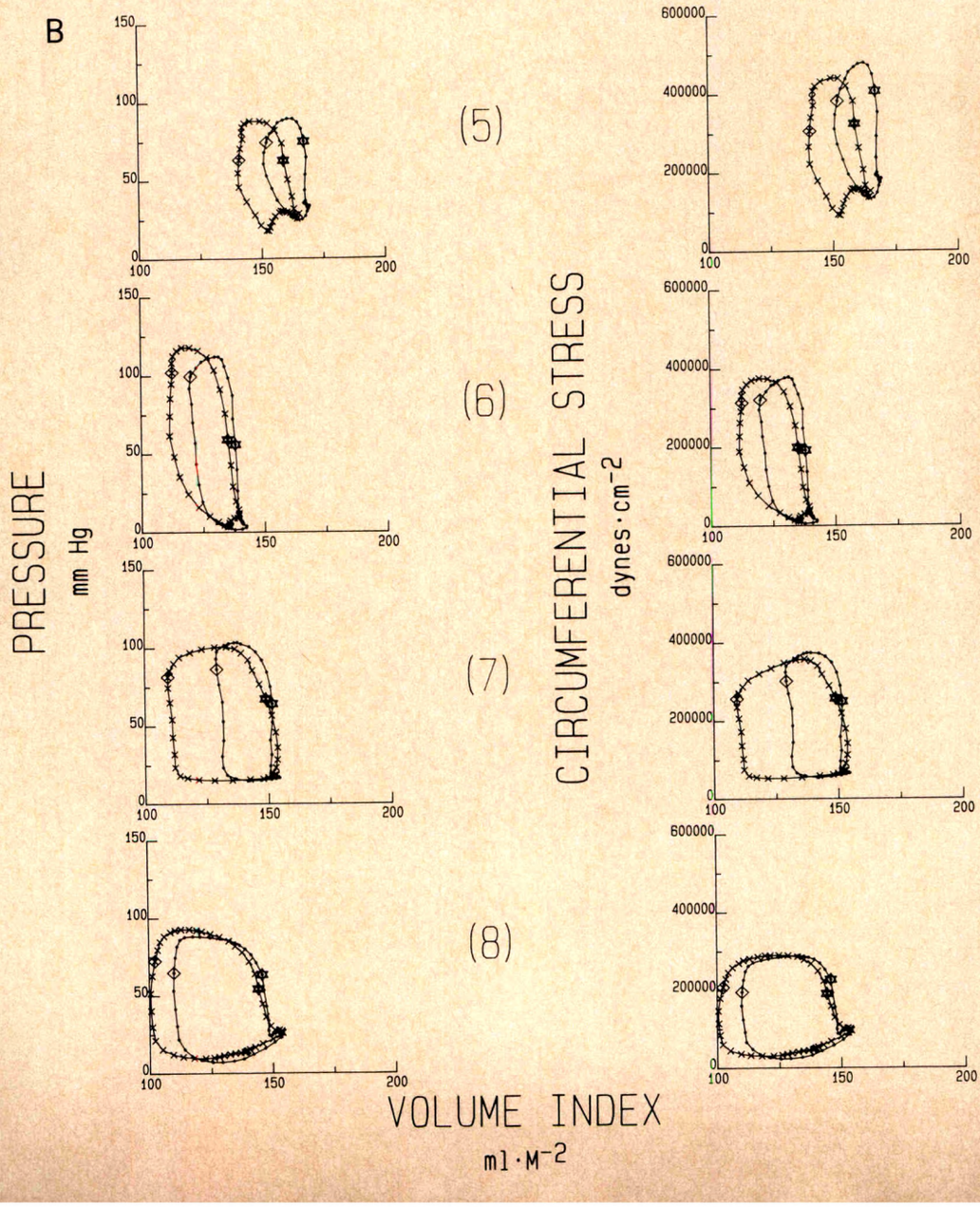
wall stress values. Patients 1 to 5 had high baseline peak wall stress, whereas patients 6 to 8 had normal baseline peak wall stress.

In the 8 patients as a group, stroke volume index and ejection fraction increased significantly after hydralazine and systemic vascular resistance and wall stress decreased. There were no changes in LV pressure, arterial pressure, end-diastolic volume index or peak dP/dt.

Patients with high peak LV wall stress differed from those with normal peak wall stress in several ways. LVEDP, arterial diastolic pressure, end-diastolic volume index and systemic vascular resistance were significantly higher in the 5 patients with high peak LV wall stress, while ejection fraction was lower. Systolic arterial and LV pressures, stroke volume and peak dP/dt were no different between patients with high and those with normal peak wall stress. The groups formed on the basis of normal or high peak wall stress are nearly the same as would be formed by separation of normal from high systemic vascular resistance or LVEDP.

Changes during hydralazine therapy also differed between patients with normal and those with high peak stress. LV and arterial diastolic and systolic pressures, LV stress and systemic vascular resistance all decreased more in patients with high peak stress. The increase in stroke volume was numerically greater in patients with high peak stress, but this difference was not significant in these 8 patients.

Pressure-volume and stress-volume points are plotted in Figure 1. Patient 2, whose heart was the most dilated, is plotted on a larger volume axis than the others. As shown in Table I, patients 1 to 5 had higher peak wall stress and more LV dilation than patients 6 to 8. Hy-



dralazine lowered LV pressure and/or diastolic volume in patients 1 to 5, but did not in patients 6 to 8. Peak systolic pressure decreased substantially in patients 1, 2 and 4 in whom hydralazine also decreased LVEDP. In patients 2, 3 and 5, LV diastolic volume decreased. In these patients, decreased diastolic volume persisted through early systole, contributing to decreased systolic volume (note displacement of right sides of loops to lower volume). Thus, both decreased LV pressure and volume decreased wall stress in patients 1 to 5. In contrast, hydralazine did not change systolic pressure or diastolic pressure-volume relations in patients 6 to 8, so that end-systolic wall stress did not decrease.

Discussion

During hydralazine therapy for idiopathic dilated cardiomyopathy, increased stroke volume resulted from decreased end-systolic volume, accompanied by decreased LV wall stress and decreased systemic resistance. Arterial and LV pressure were not significantly decreased. Our patients could be classified into 2 groups on the basis of normal or high LV stress. Patients with high LV stress had hemodynamically more severe heart failure with higher diastolic arterial pressure and LVEDP, higher LV volume, higher systemic resistance and lower stroke volume and ejection fraction than patients with normal LV stress. The severity of heart failure was not a function of patient age or of duration of symptoms.

Our findings support the conclusions of other investigators who have tried to predict the response to vasodilators in heart failure by hemodynamic stratification. Patients with higher systemic resistance or higher LVEDP respond better to vasodilators.[1] Hydralazine increases stroke volume more in patients with larger LV dimensions.[2] Although stroke volume did not increase more in our patients who had higher systemic resistance, larger LV cavities, higher LVEDP and high LV wall stress than in patients with normal wall stress, the trend toward higher stroke volume in the high stress group might have been significant with more patients.[1,2] Hydralazine decreased wall stress, LV pressure and systemic resistance more in patients with high LV wall stress than in those with normal LV stress.

Although previous workers have speculated that responsiveness to hydralazine is a function of pretreatment LV wall stress,[2] none have studied changes in wall stress, pressure-volume relations and stress-volume relations during vasodilator therapy. Our findings support the hypothesis that patients with high pretreatment LV stress respond better to vasodilators.[2] Additionally, changes in pressure- and stress-volume relations in our study explain the association between high wall stress and better response to hydralazine.[2] Vasodilator "unloading" in congestive heart failure probably acts by reducing systolic wall stress against which the failing left ventricle ejects.[3–5] In patients with high LV wall stress (loops 1 to 5), hydralazine reduces pressures (arterial pressure, LV systolic pressure and LVEDP) (loops 1, 2 and 4) or reduces end-diastolic volume (loops 2, 3 and 5). Reduced LV end-diastolic volume after hydralazine "carries through" to systole as shown by leftward displacement of the right and top portions of loops 2, 3 and 5. Because wall stress is directly proportional to LV pressure and volume (through changes in LV radius and wall thickness), either decreased LV systolic pressure or volume decreases end-systolic LV stress.[14,18] Hydralazine did not decrease LV systolic pressure and LV diastolic volume in patients with normal pretreatment LV stress (loops 6 to 8). Thus, hydralazine decreases end-systolic wall stress in patients with high pretreatment LV stress, unloading the left ventricle by effects on both ventricular pressure and volume.

Our data are not entirely consistent with the hypothesis that hydralazine increases LV stroke volume by reducing LV stress. End-systolic stress did not always decrease despite decreased end-systolic volume (loops 6 and 8). Hydalazine may also increase LV stroke volume by a direct inotropic effect. Hydralazine increases LV contractility in nonfailing ventricles.[7] In patients 6 and 8, hydralazine shifted late systolic pressure-volume relations (upper left corners of loops) toward higher pressure or wall stress despite lower volume, consistent with increased LV contractility.[4,5,19] Another index of cardiac performance, peak positive LV dP/dt, reflects changes in LV contractility in the absence of changes in LVEDP.[20–23] Although shifts in systolic pressure-volume relations in our patients suggested increased LV contractility, changes in peak LV dP/dt did not. This discrepancy may indicate relative insensitivity of LV dP/dt to changes in contractility. Alternatively, changes in late systolic pressure-volume relations may be dependent on systemic resistance, a concept that is both supported and refuted by experimental data.[24–26] Although inotropy may play a role in determining responsiveness to hydralazine in congestive heart failure, this role is probably relatively unimportant.

We conclude that hydralazine improves LV function in patients with cardiomyopathy by reducing elevated LV wall stress through reduced LV pressure and volume. Hydralazine has little inotropic effect in these patients. Further studies may establish the efficacy of hemodynamic stratification in selecting candidates for vasodilator therapy.

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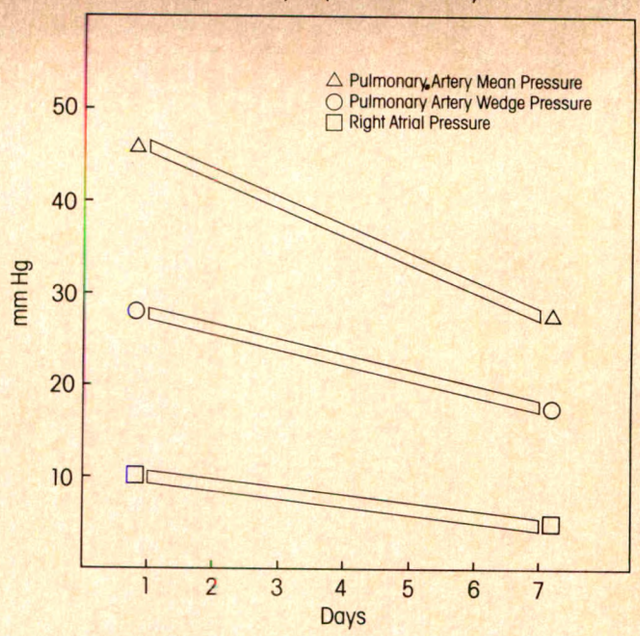

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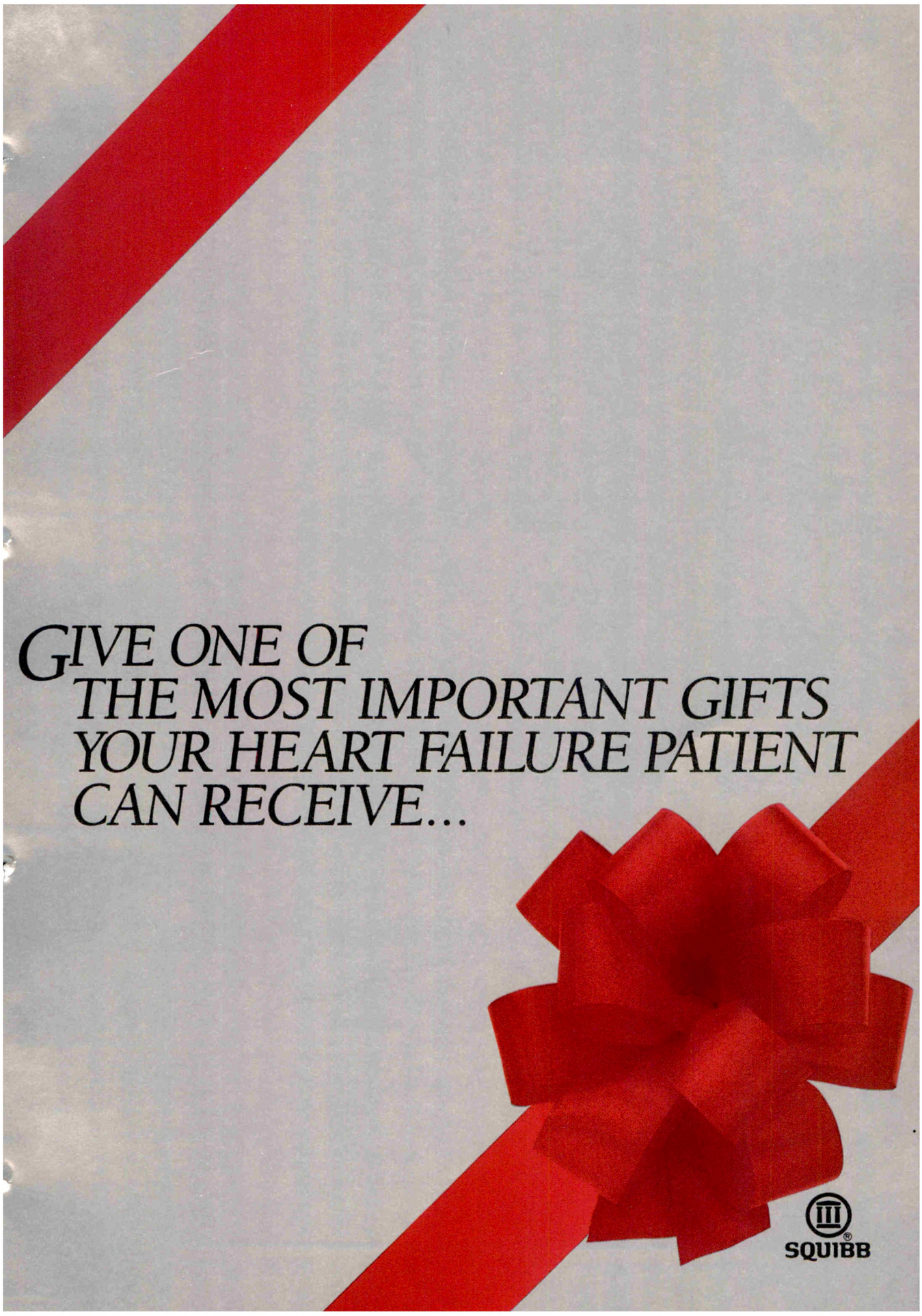

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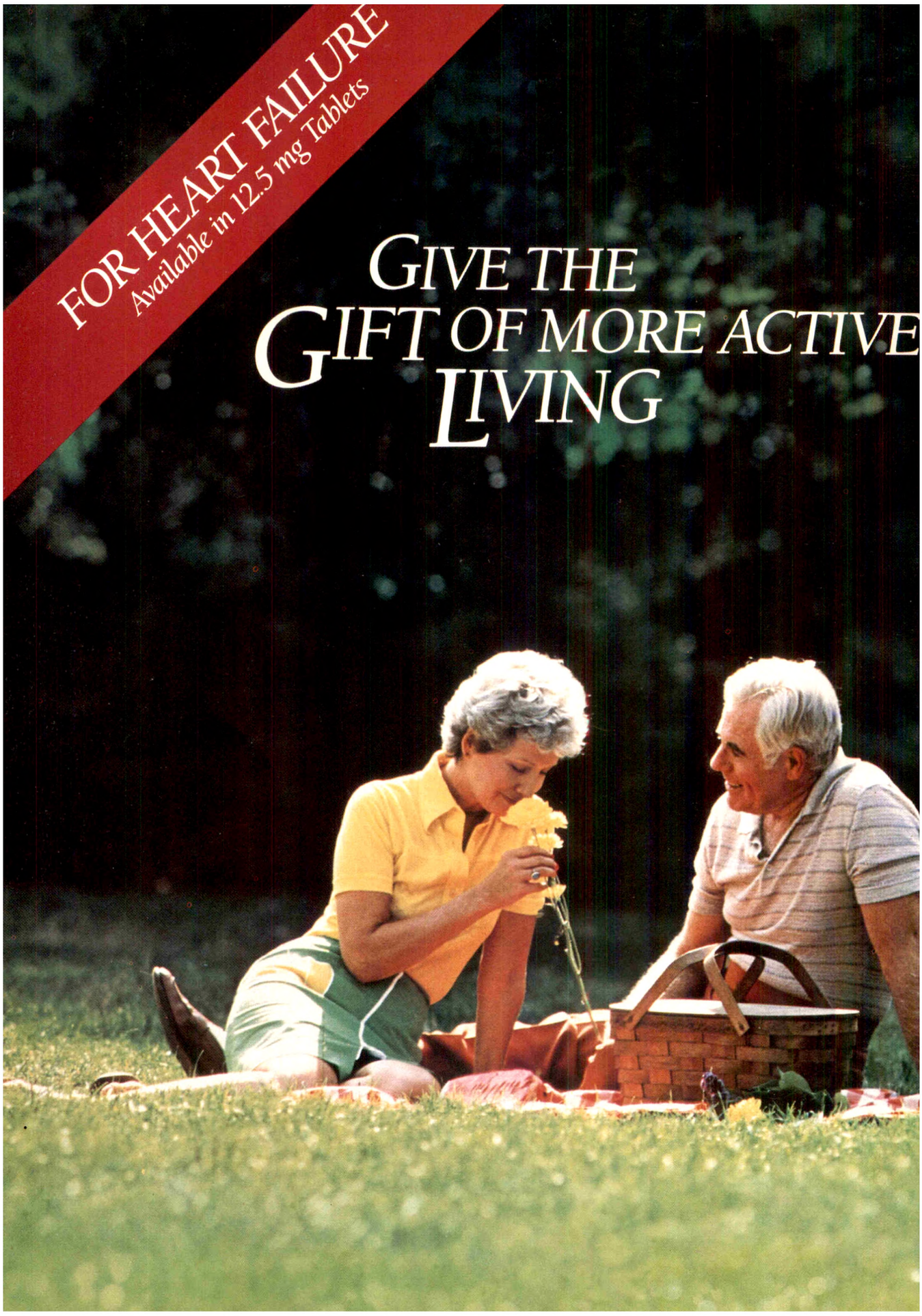
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Significantly greater improvement in dyspnea, fatigue, orthopnea, and edema with CAPOTEN than with digitalis and diuretics alone.†[1]

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A 24.3% increase after 12 weeks of CAPOTEN versus 0.4% with digitalis and diuretics alone.†[1]

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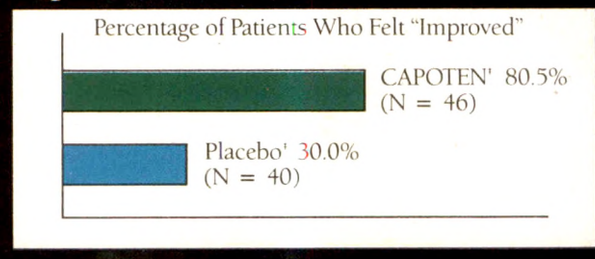

□ *Use CAPOTEN when symptoms persist despite digitalis and diuretic therapy.*

ACE*INHIBITOR

CAPOTEN® (captopril tablets) IN HEART FAILURE§

YOUR FIRST CHOICE AFTER DIGITALIS AND DIURETICS

*Angiotensin Converting Enzyme

†Ninety-two patients, refractory to but continuing on digitalis and diuretics, were given CAPOTEN or placebo for 12 weeks. Patients were primarily New York Heart Association Class II and Class III. Dosages of CAPOTEN ranged from an initial 25 mg tid to a maximum maintenance dosage of 100 mg tid.[1]

‡Given with digitalis and diuretics.

§CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs (e.g., procainamide) known to affect the white cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. See INDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

tion of blood pressure may occasionally occur within the 1st hour after administrat of the initial captopril dose in patients on diuretics, especially those recently placed diuretics, and those on severe dietary salt restriction or dialysis. This possibility be minimized by either discontinuing the diuretic or increasing the salt intake ab 1 week prior to initiation of captopril therapy or by initiating therapy with sm doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 h after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators sho be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihyperten agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may especially important in supporting blood pressure in patients receiving captoj alone or with diuretics. Beta-adrenergic blocking drugs add some further antihyperten effect to captopril, but the overall response is less than additive. Therefore, use age affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neu blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassi supplements only for documented hypokalemia, and then with caution, since th may lead to a significant increase of serum potassium. Use potassium-containing s substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroi anti-inflammatory agents may reduce the antihypertensive effect of captopril, esp cially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive ur test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year stud with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C – There are no adequate and well-controlled studies pregnant women. Embryocidal effects were observed in rabbits. Therefore, captoj should be used during pregnancy only if the potential benefit outweighs the potent risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when a ministering captopril to a nursing woman, and, in general, nursing should be interrupt

Pediatric Use: Safety and effectiveness in children have not been establish although there is limited experience with use of captopril in children from 2 mont to 15 years of age. Dosage, on a weight basis, was comparable to that used in adul Captopril should be used in children only if other measures for controlling blo pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials invo ing approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal sufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patie

Hematologic – Neutropenia/agranulocytosis have occurred (see WARNINGS). An mia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash (usually maculopapular, rarely urticarial), often with prurit and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (dependi on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, withc rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, a photosensitivity have also been reported. Angioedema of the face, mucous mei branes of the mouth, or of the extremities in about 1 of 1000 patients – reversible discontinuance of captopril therapy. One case of laryngeal edema reported. Flushi or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur, see WARNINGS and PRECAUTION (Drug Interactions) for discussion of hypotension on initiation of captopril thera Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angi pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failu each in 2 to 3 of 1000 patients.

Dysgeusia – About 2 to 4 (depending on renal status and dose) of 100 patie developed a diminution or loss of taste perception; taste impairment is reversible a usually self-limited even with continued drug use (2 to 3 months). Gastric irritatic abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulce peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspn cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did appear at increased frequency compared to placebo or other treatments used controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patie although no causal relationship has been established. Rarely cholestatic jaundice a hepatocellular injury with or without secondary cholestasis, have been reported. transient elevation of BUN and serum creatinine may occur, especially in volum depleted or renovascular hypertensive patients. In instances of rapid reduction longstanding or severely elevated blood pressure, the glomerular filtration rate m decrease transiently, also resulting in transient rises in serum creatinine and BU Small increases in serum potassium concentration frequently occur, especially patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansi with an I.V. infusion of normal saline is the treatment of choice for restoration blood pressure. Captopril may be removed from the general circulation by hemodialys

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be tak one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosa must be individualized; see DOSAGE AND ADMINISTRATION section of pac age insert for detailed information regarding dosage in hypertension and in hea failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosa adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 1 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 1 tablets.
(J3-658C)

Reference: 1. Cannon PJ, Criley JM, Dzau VJ, et al: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Col Cardiol 2:755–763, 1983.

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INNOVATORS IN CARDIOVASCULAR MEDICINE

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Left Ventricular Apical Masses: Noninvasive Differentiation of Rare from Common Ones

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Previous investigators[1–3] have described 2-dimensional echocardiographic (2-D echo) features of uncommon cardiac masses. The value of 2-D echo criteria in distinguishing these masses from thrombi has not been analyzed systematically. We designed this study to assess the usefulness and limitations of clinical and 2-D echo criteria in differentiating among distinct types of LV apical masses.

A search of our data bank for patients in whom good quality 2-D echocardiograms showing obvious masses involving the LV apical area yielded 3 patients with apical hypertrophic cardiomyopathy and 4 patients with apical tumor. We included a similar number of patients with apical thrombi for comparative analysis (Table I). The final diagnosis was reached in 10 of 11 patients by pathologic evaluation of biopsies or of the masses removed at surgery and necropsy. In a young, asymptomatic Nigerian black man (patient 6), the diagnosis was based on the presence of symmetrically inverted T waves 20 mm deep in the left precordial leads and a "spade-like" narrowing of the apical cavity on 2-D echocardiography, with localized hypertrophy of the apex.[2] The 2-D echocardiograms were recorded in the standard fashion using ultrasound imaging systems (Hewlett-Packard 77020AC or Toshiba SSH-10A) with a 2.25- or 3.5-MHz medium or short focused transducer. The criteria used to define left ventricular thrombus and apical hypertrophy were those stated in previous reports.[1–4] Apical tumor was suspected when the mass did not fulfill the criteria for either thrombus or hypertrophy and showed inhomogeneous ultrasonic appearance, demarcation from but extension into the myocardium, gross or bizarre distortion of the cardiac anatomy and presence of pericardial effusion.[1,5] The 2-D echocardiograms were also evaluated for the presence or absence of 12 specific visual characteristics.

One investigator assessed the recorded history, physical examination, standard 12-lead electrocardiogram (ECG) and chest x-ray (Table I) plus the information that an LV apical mass was present to render a diagnosis. Another investigator assessed the 2-D echocardiograms alone to render a diagnosis, and then he was given the clinical data and again asked to identify the nature of the apical mass. Neither investigator knew the pathologic findings or the proportion of patients with any diagnosis within this study group. Each investigator might choose the single correct diagnosis (+3 points), list an alternative diagnosis after (+2 points) or before (+1 point) the correct one, be unable to choose among the 3 diagnoses (0 points), list only a single but incorrect diagnosis (−1 point) or list only the 2 incorrect diagnoses (−2 points). Thus a perfect diagnosis of all 11 patients would yield

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TABLE I Clinical and Pathology Findings in 11 Patients with Left Ventricular Apical Mass

Pt	Age (yr) & Sex	History	Positive Findings (Examination, ECG, X-Ray)	Coronary Disease*	Morphology
1	69M	MI, dyspnea, syncope	CHF, MR, VT, LBBB, cardiomegaly†	LAD, right, LC	Thrombus
2	72M	MI, CVA, chest pain	Old MI, VPCs	LAD, right	Thrombus
3	62M	HBP, MI, LV aneurysm, chest pain, dyspnea, syncope	CHF, MR, old MI, VT, cardiomegaly	LAD, right LC	Thrombus
4	56M	HBP, MI, LV aneurysm, dyspnea	CHF, MR, LVH, old MI, calcified aneurysm, cardiomegaly	LAD, LC	Thrombus
5	73F	HPB, dyspnea, syncope	CHF, MR, AF, St-T changes, LVH cardiomegaly	LC	Apical hypertrophy
6	24M	Car accident	Extreme ST-T changes, LVH	—	—‡
7	60F	Bilateral mastectomy, CVA, chest pain, dyspnea	CHF, AF, VT, ST-T changes cardiomegaly	0	Apical hypertrophy
8	46F	Retroperitoneal mass, CVA, dyspnea	CHF, MR, ST-T changes, lung metastases, cardiomegaly	—	Adenocarcinoma
9	32F	Chest pain	ST-T changes, LVH, VT, cardiomegaly, apical calcifications	0	Fibroma
10	75F	MI, chest pain, dyspnea	CHF, MR, old MI, cardiomegaly, MAC	LAS	Fibroma
11	16F	Mandibular cyst, dyspnea	LBBB, VT, cardiomegaly	0	Fibroma

* Presence of ≥70% coronary obstruction.
† Cardiothoracic ratio >50%.
‡ Diagnosis of apical hypertrophy based on clinical and 2-D echo criteria (see text).
AF = atrial fibrillation; CHF = congestive heart failure; CVA = cerebrovascular accident; LC = circumflex coronary artery; HBP = high blood pressure; LAD = left anterior descending coronary artery; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MAC = mitral anulus calcification; MI = myocardial infarction; MR = mitral regurgitation; VPCs = ventricular premature complexes; VT = ventricular tachycardia; — = no information available; 0 = absent or negative.

a score of 33; the accuracy and certainty of diagnosis were expressed by a percentage score index (score/33 × 100).

The differential diagnostic accuracy of the methods used is expressed in Table II. The clinical evaluation was useful in defining patients with thrombus and with metastatic cardiac tumor. Because 88 to 99% of cardiac metastases found at necropsy have been associated with primary or secondary intrathoracic malignancy,[6] the x-ray findings of pulmonary masses in patient 8 (Table I) directed the diagnosis to cardiac tumor. Clinical assessment showed 2 major limitations: symptoms and physical examination were noncontributory; and there were no pathognomonic features to aid in recognition of primary cardiac tumors or apical hypertrophy. In 2 of our 3 patients with apical hypertrophy, the ECG showed only nonspecific ST-T changes.[3] A similar ECG pattern, however, was found in most of our patients with tumor. The 2-D echocardiogram improved recognition of apical hypertrophy. Nevertheless, all methods were imperfect in differentiating the apical tumors from thrombi.

There was lack of specificity of visual 2-D echo criteria; 6 of the 12 visual characteristics analyzed were scattered among the 3 categories of masses. These criteria were features related to the mass: strictly apical, symmetric, smooth free edges and presence of calcified areas; and absence of apical diameter narrowing and pericardial effusion. Table III includes the other 6 characteristics that were present in all patients in at least 1 category of mass, although not confined to 1 category necessarily. Wall motion patterns adjacent to and remote from the mass were found to differ in the 3 categories. Patients with thrombus had both local akinesia/diskinesia and abnormal wall motion in areas remote from the mass. All 4 patients with tumor had normal wall motion remote from the apex and 3 of these had severe apical asynergy. All patients with apical hypertrophy had mild apical hypokinesia and normal remote wall motion. Patients with apical hypertrophy had all 6 characteristics listed in Table III in common (i.e., the feature was either present or absent in all). Moreover, active contractility of the mass was a finding specific for these patients, probably representing the major differential diagnostic criterion compared with other categories of apical masses. Our results confirmed the presence of previously described criteria in all patients with thrombi, but revealed their lack of specificity owing to frequent occurrence in patients with tumors. The finding of an apical mass that is visible throughout the cardiac cycle, has clear demarcation from the myocardium adjacent to an area of severe myocardial asynergy,[1,4] and is without active contractility of the mass during systole was present in all of our patients with thrombi, but also was seen in 3 patients with apical tumor (Fig. 1).

These results support the combined use of clinical and 2-D echo data for optimal diagnosis of left ventricular apical masses but additionally suggest the need

TABLE II Diagnostic Accuracy* of Methods Used in Differentiating Left Ventricular Apical Masses

	Thrombus (n = 4)	Apical Hypertrophy (n = 3)	Tumor (n = 4)	Total (n = 11)
Method				
Clinical	100%	44%	50%	70%
2-D echo	100%	88%	50%	78%
2-D echo + clinical	100%	88%	75%	88%

* The diagnostic accuracy is represented for each method studied as achieved score/maximal perfect score × 100 (see text).
2-D echo = 2-dimensional echocardiography.

TABLE III Two-Dimensional Echocardiographic Visual Criteria

	Thrombus	Apical Hypertrophy	Tumor
Abnormal adjacent wall motion	+(A/D)	+(H)	+(H/A/D)
Abnormal remote wall motion	+	0	0
Mass: demarcated from myocardium	+	0	VP
Mass: active contractility	0	+	0
Mass texture			
Different from the myocardium	VP	0	VP
Nonuniform	VP	0	VP

A = akinesia; D = dyskinesia; H = hypokinesia; 0 = absent or negative; VP = characteristic variable but present in most patients in a group; + = present in all patients.

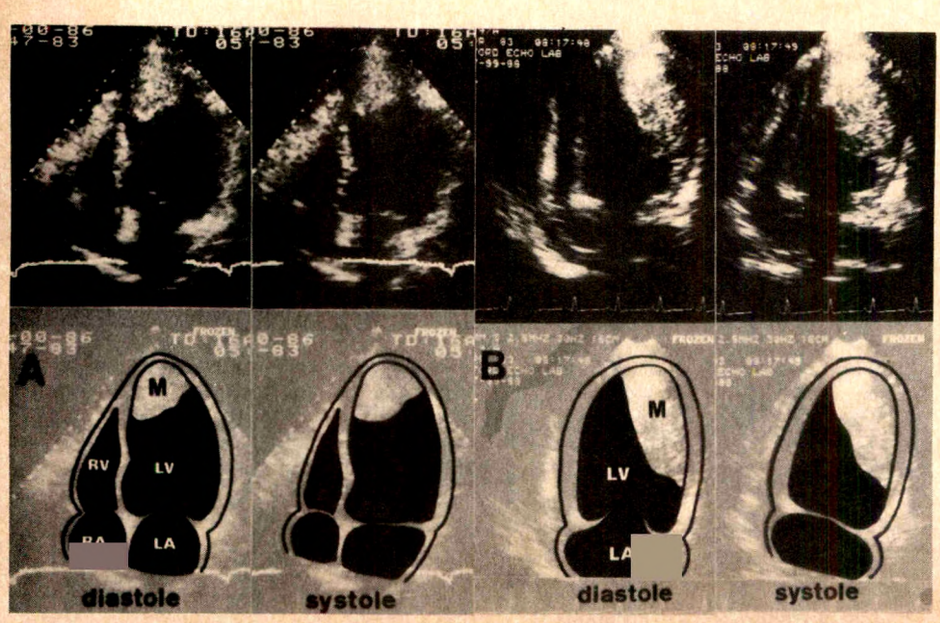

FIGURE 1. Two-dimensional echocardiograms recorded in the apical 4-chamber view in patients with thrombus (**A**) and tumor (**B**). The masses (M) show very similar visual texture characteristics and both are demarcated from the akinetic myocardium. The wall motion remote from the mass was abnormal in **A** and normal in **B.** LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

for improved 2-D echo or other tissue characterization methods to provide more direct information and better segregation of tumors from thrombi. Our few patients with apical hypertrophic cardiomyopathy had several group characteristic 2-D echo features that may help differentiate this entity from apical thrombi.

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Pericardial Defect Mimicking a Left Atrial Mass

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Left atrial (LA) tumor and thrombus are the most common causes of abnormal intraatrial echoes. Extracavitary echoes mimicking intracardiac masses have not been reported. We report a patient with a pericardial defect in whom post-traumatic pericardial adhesions were responsible for the echocardiographic appearance of an LA mass.

A 23-year-old man was referred for 3-artery systolic myocardial bridging. The patient had a 1-year history of retrosternal chest pain after an automobile accident. Examination and chest x-ray were normal. The electrocardiogram displayed a sinus rhythm, a PR interval of 0.24 second and right-axis deviation (160°). Two-dimensional echocardiography (long-axis and subxiphoid views) suggested a large mass fixed to the posterior LA wall behind the posterior mitral valve leaflet (Fig. 1 and 2). The patient underwent incision of the myocardial bridging and LA exploration. No intracavitary mass was visualized or palpated. However, a large, round posterior pericardial defect was seen with the pericardial rim adherent to and compressing the LA wall. Adhesions were lysed between the left atrium and parietal pericardium. A coronary artery bypass graft to the distal circumflex and incision of the left anterior descending myocardial bridge was performed.

Echocardiography had enhanced the clinical ability to recognize intracardiac masses and may have greater sensitivity than any other diagnostic technique.[1] Although false-positive and false-negative studies are occasionally encountered using M-mode echocardiography,[2,3] 2-dimensional techniques tend to clarify confusing studies. In this case we postulate that post-traumatic inflammatory changes in the pericardium contribute to fibrosis and adhesions between the edge of the pericardial defect and left atrium. An extrinsic compressive effect on the posterior left atrium by the fibrotic tissue led to the echocardiographic appearance of a nonmobile LA mass behind the posterior mitral leaflet. The appearance of the pericardial defect suggested a congenital origin. We believe that this is the first reported case of a pericardial defect presenting as an LA mass.

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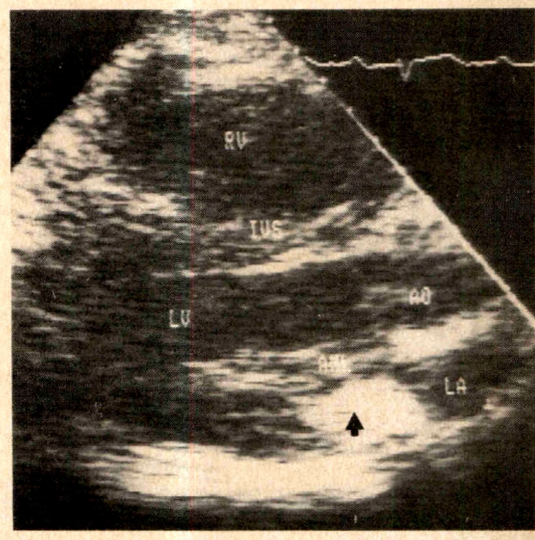

FIGURE 1. Two-dimensional echocardiogram—parasternal long-axis view. AML = anterior mitral leaflet; AO = aortic root; IVS = interventricular septum; LA = left atrium; LV = left ventricle; RV = right ventricle; ↑ = left atrial echoes suggestive of a mass lesion.

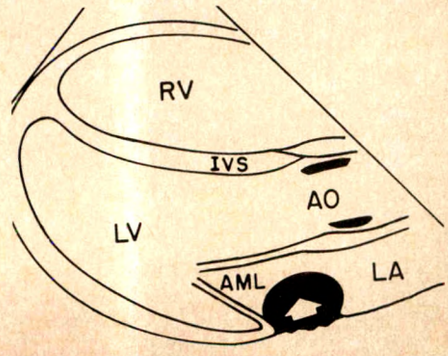

FIGURE 2. Schematic representation of Figure 1. Abbreviations as in Figure 1.

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Mitral Valve Prolapse, Wolff-Parkinson-White Syndrome, His Bundle Sclerosis and Sudden Death

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Case reports of association of mitral valve prolapse (MVP) and Wolff-Parkinson-White syndrome (WPW),[1] of MVP and atrioventricular (AV) block[2] and of WPW and AV block[3] are rare. Reports of sudden death in patients with WPW[4] or MVP[5–8] are also uncommon.

A 19-year-old man who had previously complained of palpitations was admitted to the emergency room for cardiac arrest. Protracted attempts at resuscitation were unsuccessful. An electrocardiogram was not recorded. The only existing electrocardiogram, taken 4 years earlier, showed WPW syndrome type A (Rosenbaum classification) was observed (Fig. 1). Witnesses stated that the patient complained of violent chest pain after being pushed into a swimming pool and then lost consciousness. Postmortem examination of brain, lungs, liver, spleen, adrenal glands, kidneys and digestive tract was normal. Heart examination showed a floppy mitral valve (Fig. 2) and fibrosclerosis of the His bundle.

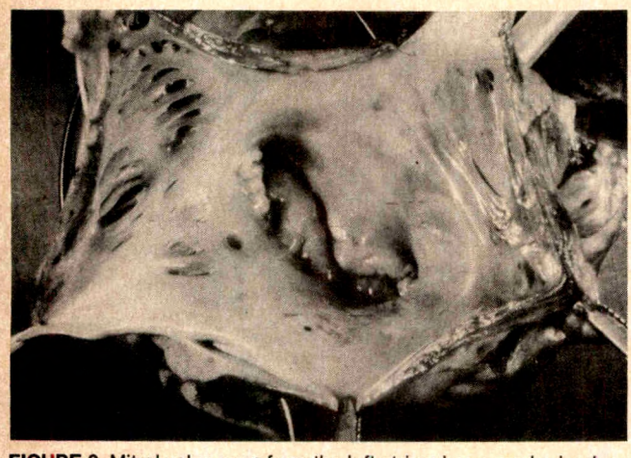

FIGURE 2. Mitral valve seen from the left atrium has a marked redundancy and ballooning of the posterior leaflet.

From the Department of Cardiology, Croix-Rousse Hospital, and the Department of Pathology, Louis Pradel Hospital, at the University Claude Bernard, UER Lyon-Nord and Alexis Carrel, Lyon, France, and from the Cardiac Rehabilitation Center, 69260 Charbonnières-les-Bains, France.

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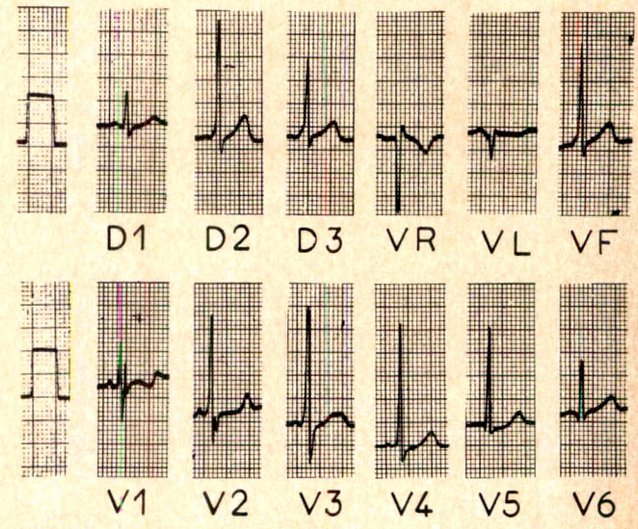

FIGURE 1. Electrocardiogram recorded 4 years before death showing Wolff-Parkinson-White syndrome type A (Rosenbaum classification). Sinus rhythm is 65 beats/min. P-delta = 100 ms; delta wave duration = 50 ms; delta wave positive in V_1, V_2, D_2, D_3 and aVF; negative in aVL.

To our knowledge the association of MVP, WPW syndrome, and His bundle sclerosis has not been described. Is this pathologic association fortuitous or does it indicate a common embryologic origin? No direct relation between MVP and WPW, nor between WPW and AV block has been established. The association between a MVP and involvement of the conduction system, recently reported by Bharati et al,[7] suggests relation between these 2 abnormalities.

Acknowledgment: We thank R. Crane, PhD, and J. Pearson, MD, for their help with translation, and R.M. Jeresaty, MD, Professor of Medicine, University of Connecticut School of Medicine, Hartford, for his critical review of the manuscript.

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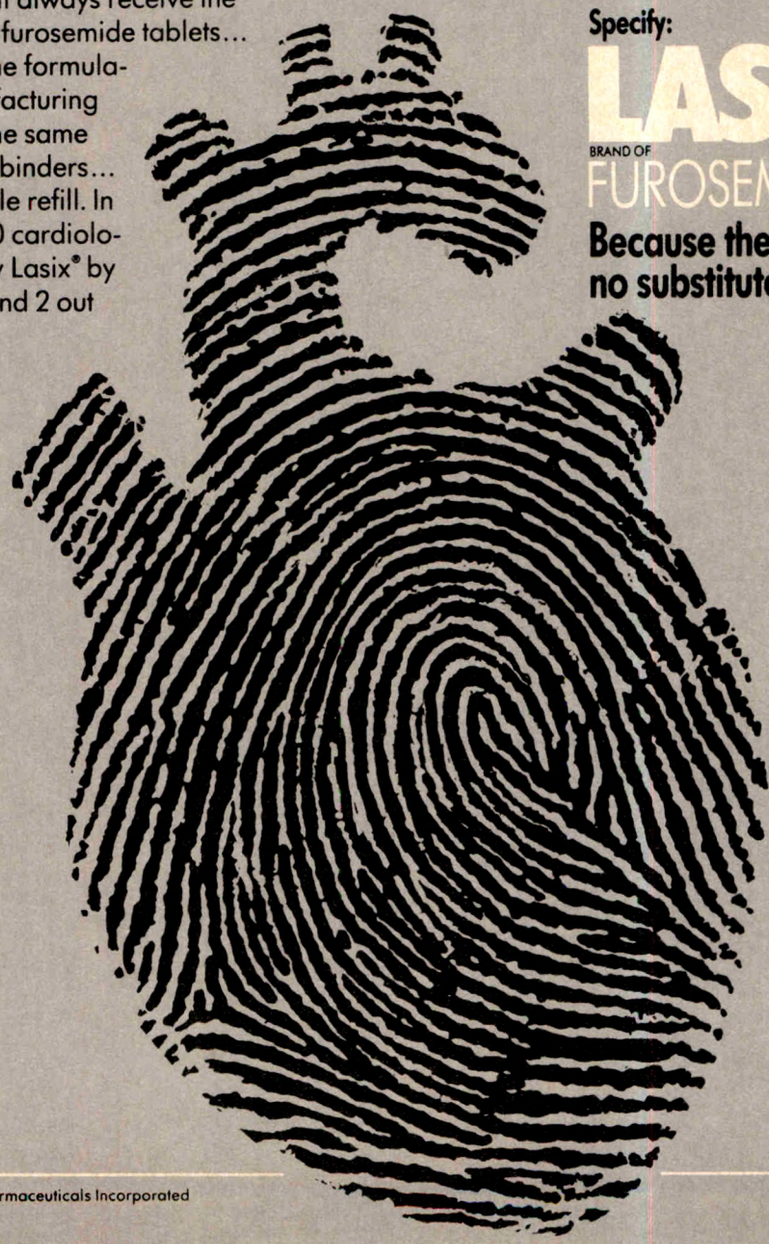

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INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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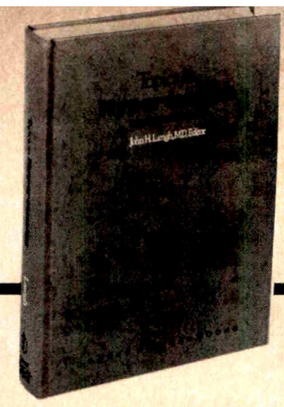

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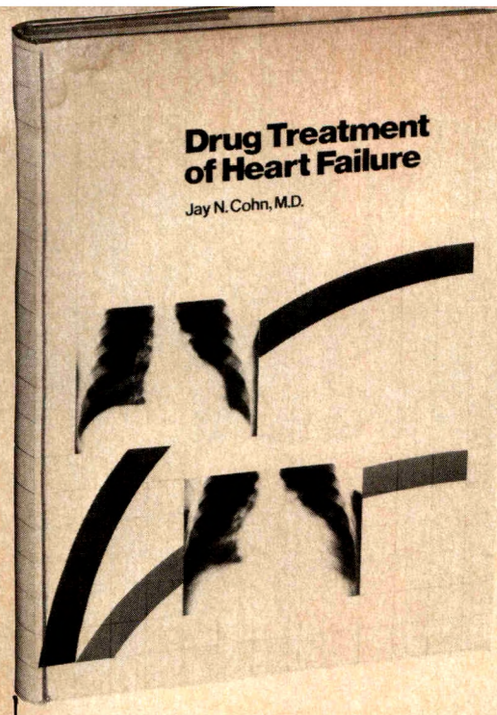

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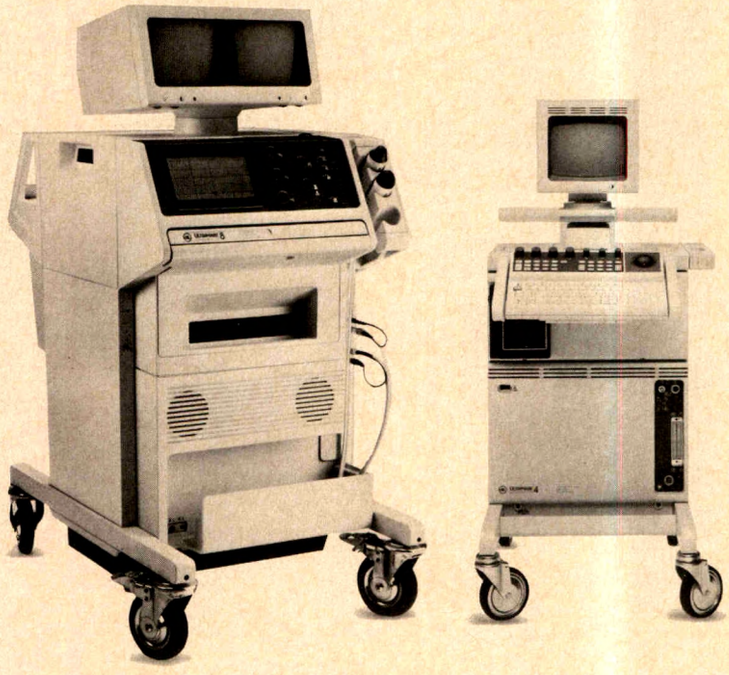

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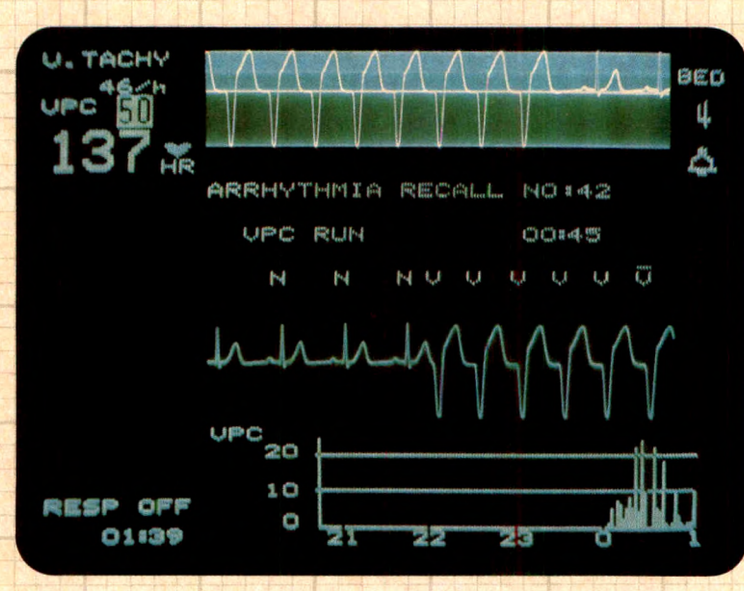

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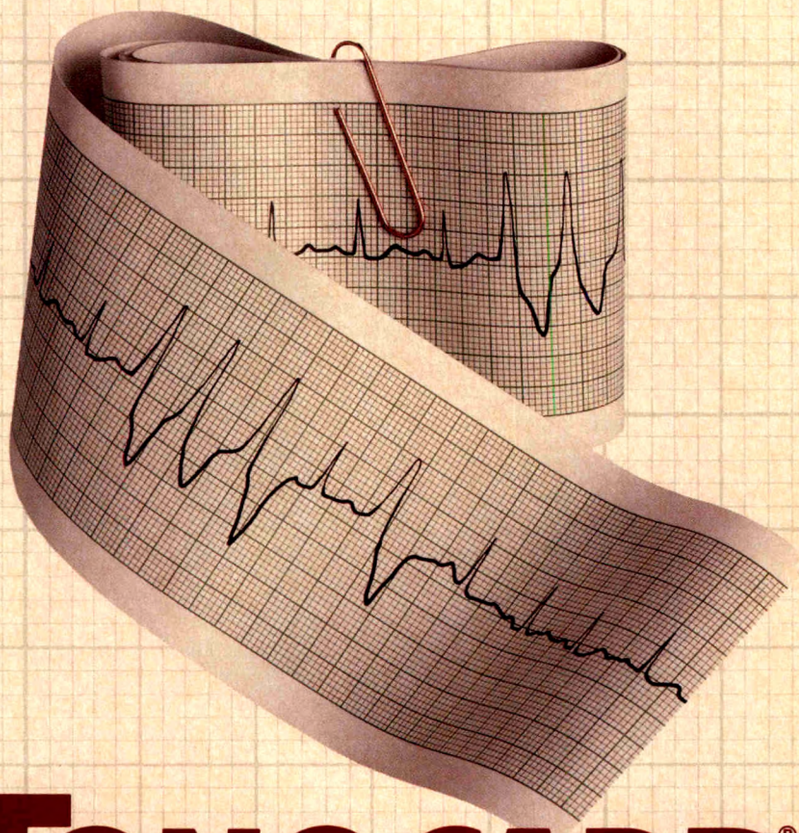

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Like other antiarrhythmics, tocainide has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given tocainide be evaluated electrocardiographically and clinically prior to, and during, tocainide therapy to determine whether the response to tocainide supports continued treatment.

CONTRAINDICATIONS

Patients who are hypersensitive to this product or to local anesthetics of the amide type.

Patients with second or third degree atrioventricular block in the absence of an artificial ventricular pacemaker.

WARNINGS

Blood Dyscrasias: Agranulocytosis, bone marrow depression, leukopenia, hypoplastic anemia and thrombocytopenia have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill and who were receiving concomitant drugs; fatalities have occurred. Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that blood counts, including differential and platelet counts, be performed at least once within the first two to three weeks of therapy; and periodically thereafter, particularly within the first three months of therapy. Blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat, or stomatitis), bruising, or bleeding. If any of these hematologic disorders is identified, TONOCARD should be discontinued and appropriate treatment should be instituted if necessary. Blood counts usually return to normal within one month of discontinuation. Caution should be used in patients with preexisting marrow failure or cytopenia of any type. (See ADVERSE REACTIONS).

Acceleration of Ventricular Rate: Acceleration of ventricular rate occurs infrequently when antiarrhythmics are administered to patients with atrial flutter or fibrillation (see ADVERSE REACTIONS).

PRECAUTIONS

General

Pulmonary Fibrosis: Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill. The experiences are usually characterized by bilateral infiltrates on x-ray and are frequently associated with dyspnea and cough. Fever may or may not be present. Patients should be instructed to promptly report the development of any pulmonary symptoms such as exertional dyspnea, cough or wheezing. Chest x-rays are advisable at that time. If these pulmonary disorders develop, TONOCARD should be discontinued. (See ADVERSE REACTIONS).

In patients with known heart failure or minimal cardiac reserve, TONOCARD should be used with caution because of the potential for aggravating the degree of heart failure.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing depression of cardiac conductivity.

In patients with severe liver or kidney disease, the rate of drug elimination may be significantly decreased (see DOSAGE AND ADMINISTRATION).

Since antiarrhythmic drugs may be ineffective in patients with hypokalemia, the possibility of a potassium deficit should be explored and, if present, the deficit should be corrected.

Like all other oral antiarrhythmics, TONOCARD has been reported to increase arrhythmias in some patients (see ADVERSE REACTIONS).

Information for Patients

Patients should be instructed to promptly report the development of bruising or bleeding; any signs of infections such as fever, chills, sore throat, or soreness and ulcers in the mouth; or any pulmonary symptoms, such as exertional dyspnea, cough, or wheezing.

Laboratory Tests

As with other antiarrhythmics, abnormal liver function tests, particularly in the early stages of therapy, have been reported. Periodic monitoring of liver function should be considered. Hepatitis and jaundice have been reported in some patients.

Drug Interactions

Specific interaction studies with digoxin and metoprolol have been conducted, no clinically significant interaction was seen with digoxin, but tocainide and metaprolol had additive effects on wedge pressure and cardiac index. TONOCARD has also been used in open studies with digitalis, beta-blocking agents, other antiarrhythmic agents, anticoagulants, and diuretics, without evidence of clinically significant interactions. Nevertheless, caution should be exercised in the use of multiple drug therapy.

TONOCARD is equally effective in digitalized and non-digitalized patients. In 17 patients with refractory ventricular arrhythmias on concomitant therapy, serum digoxin levels (1.1 ± 0.4 ng/mL) remained in the expected normal range (0.5-2.5 ng/mL) during tocainide administration.

Pregnancy

Pregnancy Category C. In a teratogenicity study in rabbits, tocainide was administered orally at doses of 25, 50, and 100 mg/kg/day (about 1 to 4 times the usual human dose). No evidence of a drug-related teratogenic effect was noted; however, these doses were maternotoxic and produced a dose-related increase in abortions and stillbirths. In a teratogenicity study in rats, an oral dose of 300 mg/kg/day (about 12 times the usual human dose) showed no evidence of treatment-related fetal malformations, but maternotoxicity and an increase in fetal resorptions were noted. An oral dose of 30 mg/kg/day (about twice the usual human dose) did not produce any adverse effects.

In reproduction studies in rats at maternotoxic oral doses of 200 and 300 mg/kg/day (about 8 and 12 times the usual human dose, respectively), dystocia, and delayed parturition occurred which was accompanied by an increase in stillbirths and decreased survival in offspring during the first week postpartum. Growth and viability of surviving offspring were not affected for the remainder of the lactation period.

There are no adequate and well-controlled studies in pregnant women. TONOCARD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether tocainide is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from TONOCARD, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

TONOCARD commonly produces minor, transient, nervous system and gastrointestinal adverse reactions, but is otherwise generally well tolerated. TONOCARD has been evaluated in both short-term (n = 1,358) and long-term (n = 262) controlled studies as well as a compassionate use program. Dosages were lower in most of the controlled studies (1200 mg/day) and higher in the compassionate use program (1800 mg and more). In long-term (2-6 months) controlled studies, the most frequent adverse reactions were lightheadedness/dizziness (15.3 percent), nausea (14.5 percent), paresthesia/numbness (9.2 percent), and tremor (8.4 percent). These reactions were generally mild, transient, dose-related and reversible with a reduction in dosage, by taking the drug with food, or by therapy discontinuation. Tremor, when present, may be useful as a clinical indicator that the maximum dose is being approached. Adverse reactions leading to therapy discontinuation occurred in 21 percent of patients in long-term controlled trials and were usually related to the nervous system or gastrointestinal system.

Adverse reactions occurring in greater than one percent of patients from the short-term and long-term controlled studies appear in the following table:

	Percent of Patients Controlled Studies	
	Short-term (n = 1,358)	Long-term (n = 262)
NERVOUS SYSTEM		
Lightheadedness/ dizziness/vertigo/ giddiness	8.0	15.3
Parasthesia/ numbness	3.5	9.2
Tremor/quivering/ tremulousness	2.9	8.4
Confusion/ disorientation/ hallucinations	2.1	2.7
Altered mood/ awareness	1.5	3.4
Restlessness/ shakiness/ nervousness	1.5	0.4
Blurred vision/visual disturbances	1.3	1.5
Discoordination/ unsteadiness/ walking disturbances	1.2	0.0
Anxiety	1.1	1.5
Tinnitus/hearing loss	0.4	1.5
Ataxia	0.2	3.0
Nystagmus	0.0	1.1
GASTROINTESTINAL SYSTEM		
Nausea	15.2	14.5
Vomiting	8.3	4.6
Anorexia	1.2	1.9
Diarrhea/loose stools	0.0	3.8
CARDIOVASCULAR SYSTEM		
Hypotension	3.4	2.7
Bradycardia	1.8	0.4
Palpitations	1.8	0.4
Chest Pain	1.6	0.4
Conduction disturbances	1.5	0.0
Left ventricular failure	1.4	0.0
OTHER		
Sweating/cold sweat/ night sweats/ clammy	5.1	2.3
Headache	2.1	4.6
Tiredness/drowsiness/ fatigue/lethargy/ lassitude/ sleepiness	1.6	0.8
Hot/cold feelings	0.5	1.5
Rash/skin lesion	0.4	8.4

An additional group of about 2,000 patients has been treated in a program allowing for the use of TONOCARD under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy, and comparatively high doses of TONOCARD were used. Fifty-four percent of the patients continued in the program for one year or longer, and 12 percent were treated for longer than three years, with the longest duration of therapy being nine years. Adverse reactions leading to therapy discontinuation occurred in 12 percent of patients (usually central nervous system effects or rash). A tabulation of adverse reactions occurring in one percent or more of patients follows:

	Percent of Patients Compassionate Use (n = 1,927)
NERVOUS SYSTEM	
Lightheadedness/dizziness/ vertigo/giddiness	25.3
Tremor/quivering/ tremulousness	21.6
Restlessness/shakiness/ nervousness	11.5
Confusion/disorientation/ hallucinations	11.2
Altered mood/awareness	11.0
Ataxia	10.8
Blurred vision/visual disturbances	10.0
Paresthesia/numbness	9.2
Nystagmus	1.1
GASTROINTESTINAL SYSTEM	
Nausea	24.6
Anorexia	11.3
Vomiting	9.0
Diarrhea/loose stools	6.8
CARDIOVASCULAR SYSTEM	
Increased ventricular arrhythmias/PVCs	10.9
CHF/progression of CHF	4.0
Tachycardia	3.2
Hypotension	1.8
Conduction disturbances	1.3
Bradycardia	1.0
OTHER	
Rash/skin lesion	12.2
Sweating/cold sweat/night sweats/clammy	8.3
Arthritis/arthralgia	4.7
Myalgia	1.7
Lupus	1.6

Adverse reactions occurring in less tha one percent of patients in either the co trolled studies or the compassionate use pr gram or since the drug was marketed are follows:

Nervous System: Coma, convulsions/s zures, depression, psychosis, mental chang agitation, altered taste/smell, difficulty co centrating, diplopia, dysarthria, impair memory, increased stuttering/slurred speec insomia/sleeping disturbance, local ane thesia, nightmares, thirst, weakness, mya thenia gravis.

Gastrointestinal System: Abnormal liv function tests, hepatitis, jaundice, (see PR CAUTIONS); stomatitis; abdominal pain/d comfort; constipation; dysphagia; gastroi testinal symptoms (including dyspepsia).

Cardiovascular System: Ventricular fib lation, extension of acute myocardial infar tion, cardiogenic shock, angina, AV bloc hypertension, increased QRS duratio pleurisy/pericarditis, prolonged QT interv right bundle branch block, syncope, vas vagal episodes, cardiomegaly, sinus arrest.

Pulmonary System: Respiratory arre pulmonary edema, pulmonary embolism, p monary fibrosis, fibrosing alveolitis, interstit pneumonitis, pneumonia, dyspnea.

Other: Hematologic disorder (agranuloc tosis, bone marrow depression, hypoplas anemia, anemia, leukopenia, thrombocyt penia), increased ANA, urinary retentio polyuria/increased diuresis, alopecia, ci chonism, claudication, cold extremities, d mouth, earache, edema, fever, hiccups, itc ing, leg cramps, malaise, metallic/menth taste, muscle twitching/spasm, neck pa pain radiating from neck, pallor/flushed fac pressure on shoulder, yawning.

Agranulocytosis, bone marrow depressio leukopenia, hypoplastic anemia, and thromb cytopenia have been reported (0.18 percer in patients receiving TONOCARD in controlle trials and the compassionate use prograr Many of these events occurred in patien who were seriously ill or who were rece ing concomitant drugs; fatalities hav occurred. Most of these events have bee noted during the first 12 weeks of therap (See WARNINGS).

Pulmonary fibrosis, interstitial pneumoniti fibrosing alveolitis, pulmonary edema, an pneumonia, possibly drug related, have bee reported in patients receiving TONOCARI The incidence of pulmonary fibrosis (includir interstitial pneumonitis and fibrosing alveoliti was 0.11 percent in controlled trials and th compassionate use program. These even usually occurred in seriously ill patient Symptoms of these pulmonary disorders an or x-ray changes usually occurred followir 3-18 weeks of therapy and two patients die (See PRECAUTIONS).

HOW SUPPLIED

Tablets containing 400 mg (scored) or 600 m in bottles of 100 and unit-dose packages c 100.

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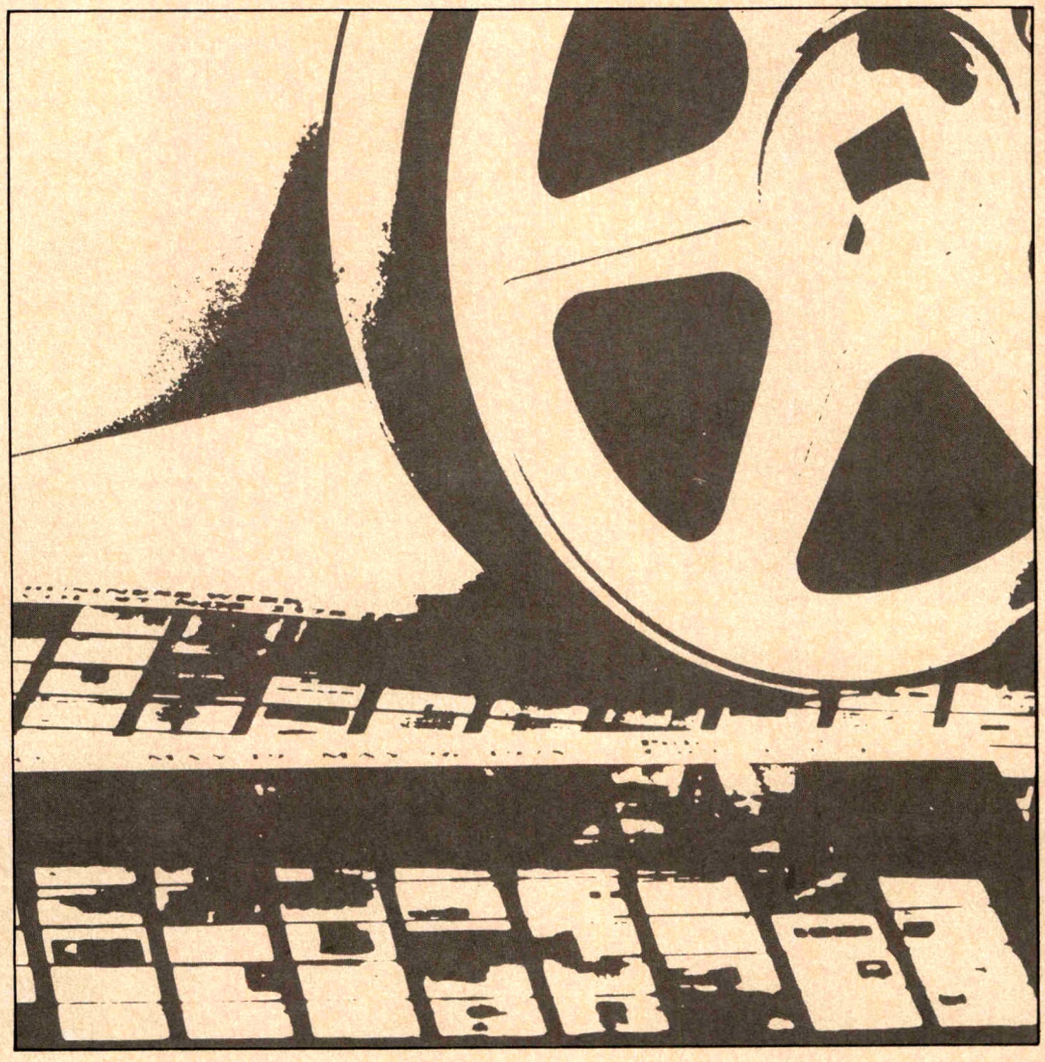

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Digoxin therapy with tablets may be compromised by:

☐ many commonly coadministered drugs, eg, antibiotics, antidiarrheals, antacids, and agents that increase or decrease gut motility

☐ concurrent GI disease: diarrhea, malabsorption syndromes, intestinal diseases, constipation

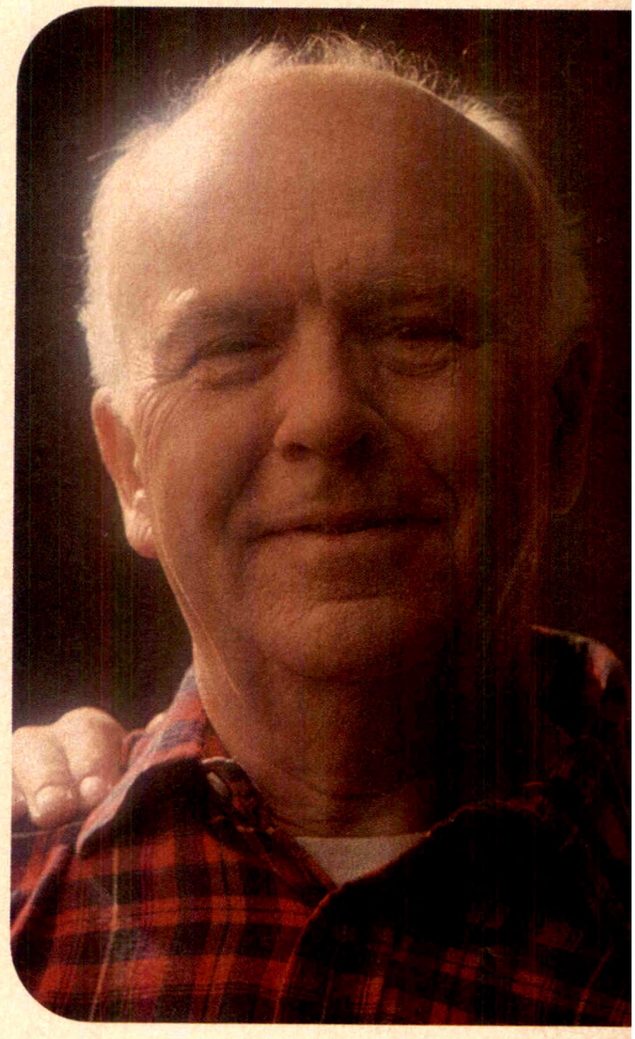
Digoxin therapy with Lanoxicaps® (digoxin solution in capsules) allows the digoxin to be much more rapidly and completely absorbed. Whereas tablet bioavailability is only in the range of 60% to 80%, bioavailability with Lanoxicaps is similar to that following IV administration, 90% to 100%. *Less variability in the amount of digoxin absorbed means less risk of over- or under-digitalization, improving your patient's safety margin.*

"Bioavailability of digoxin has represented one of the most discussed topics of cardiovascular pharmacology of the past decade. The consequent changes in pharmaceutical manufacturing have led to preparations with nearly optimal bioavailability thus favouring a substantial advancement towards a safer treatment."

Levy G, cited by Malini PL, Strocchi E, Negroni S, et al: Greater bioavailability of digoxin in a new capsule preparation. *Current Therapeutic Research* 1983;33:646-650.

"Data collected so far show that if a product is fully bioavailable, the bioavailability in different subjects and in the same subject at different times is within a very narrow range, say 95—100%. However, if a poorly available product has an *average* bioavailability of say 50%, the range in individual patients, and in the same patient at different times, covers a tremendous range, sometimes from 0 to 100%!"

Wagner JG: An overview of the analysis and interpretation of bioavailability studies in man. *Pharmacology* 1972;8:102-117.



The new standard in digoxin

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Please see brief summary of prescribing information on following page.

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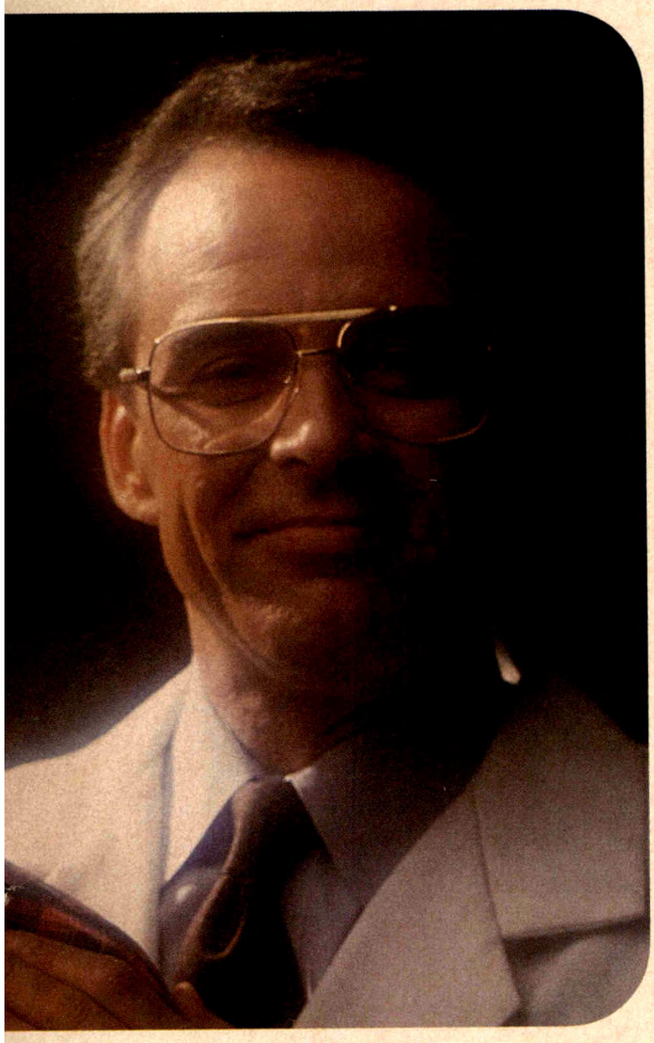


"The enhanced bioavailability of the capsule formulation and the resulting minimized intersubject and intrasubject variability in serum digoxin concentrations make the capsule dosage form the preferred form of oral digoxin for use in patients who typically have a multitude of factors that can markedly alter digoxin bioavailability."

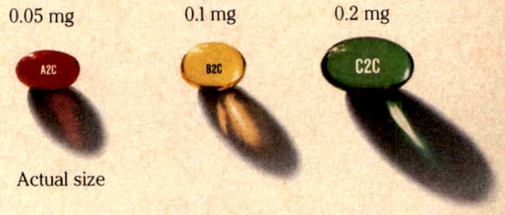
Johnson BF: Influences of dosage form and other factors on variability in digoxin absorption, in *Digoxin Therapy: The Role of Lanoxicaps®*. Burroughs Wellcome Co., 1983, pp 14-19.

"The more incompletely a drug is absorbed, the more will its absorption vary between patients and in the same patient with time. Drug formulation should always strive for the most complete bioavailability . . . ."

Koch-Weser J: Drug therapy: Bioavailability of drugs (second of two parts). *N Engl J Med* 1974;291:503-506.

Monograph Available

To receive a compilation of clinical studies, entitled *Digoxin Therapy: The Role of Lanoxicaps®*, just ask your B.W. Co.® representative or write: Lanoxicaps Monograph, Burroughs Wellcome Co., Research Triangle Park, NC 27709.



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Brief Summary of Prescribing Information

Before using Lanoxicaps® (digoxin solution in capsules), the physician should be thoroughly familiar with the basic pharmacology of this drug as well as its drug interactions and its indications and usage.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in ventricular fibrillation. Any untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS: The use of digoxin or other digitalis glycosides in the treatment of obesity is unwarranted and dangerous.

It is recommended that digoxin in soft capsules be administered in divided daily doses to minimize any potential adverse reactions. Where compliance is considered a problem, single daily dosing may be appropriate (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary. Careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS:

General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section in complete prescribing information). More time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range", because potassium depletion sensitizes the myocardium to digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section in complete prescribing information).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Hypocalcemia can nullify the effects of digoxin in man; digoxin may be ineffective until serum calcium is restored to normal.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine and verapamil cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized.

Certain antibiotics may increase digoxin absorption in patients who convert digoxin to inactive metabolites in the gut (see Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section in complete prescribing information). The magnitude of rise in serum digoxin concentration may be as much as two-fold in some cases. This interaction is significantly reduced if digoxin is given as Lanoxicaps.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g. hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e. Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sino-atrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias. *Quinidine* and *verapamil* cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain *antibiotics* increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine* and certain *anticancer drugs* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias, because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although β adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% being considered serious (1 to 4% of patients receiving digoxin). Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:

Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage. Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances.

Gastrointestinal—Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdosage. Uncontrolled heart failure may also produce such symptoms.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, apathy and psychosis can occur.

Other—Gynecomastia is occasionally observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

84-LNC-1

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The AJC in October 1960

RICHARD E. CLARK, MD

The October 1960 issue of the AJC covered 155 pages, 135 of which were used for scientific articles. Two-thirds of the issue (82 pages) was used for a symposium on anesthesia for cardiac surgery. One must recall that this was an emerging clinical speciality in an era of a mortality rate that was approximately 20%.[1] The symposium had contributions by 14 centers then engaged in open-heart surgery. These reports came from Boston, New York, Los Angeles, Cleveland, Durham, Miami, Washington, D.C., Philadelphia and Baltimore. A major concern during this period was the myocardial depressant effects of the various anesthetic agents customarily used for other types of patients and operations.

These anesthetic agents—diethyl ether, halothane, thiopental sodium and cyclopropane—were the principal agents being tested on isolated hearts, in dogs and in an uncontrolled nonrandomized way in patients. The additive effects of induction, premedication agents and relaxants also were studied.

In the laboratory, it was evident that light anesthesia made little change in right ventricular stroke volume and left ventricular stroke work.[2] Clinically, however, deeper planes of anesthesia were required and untoward effects were observed. A combination of ether and barbiturate and a parasympathetic antagonist caused a decrease in heart rate, an increase in stroke volume, and an increase in blood pressure and total peripheral resistance, with a mild to moderate decrease in cardiac output. Depressive effects particularly those of diethyl ether, cyclopropane and halothane were concentration-dependent.

Each unit appeared to adopt special monitors for measurement of a variety of variables in cardiac surgery. Among these were a variety of signal conditioners and recorders for the measurement of the electrocardiogram, the electroencephalogram, and various pressures as well as an enormous effort for the measurement of whole blood pH, P_{CO_2}, and P_{O_2} and temperature in various locations in the body. Blood gas analyzers were in their infancy. These devices required an incredible amount of technical skill to calibrate both pH and P_{CO_2} over a wide range. The physiologic importance of correction of values to 37°C had not been appreciated nor the fact that hypothermic animals became alkalotic.

Although rarely used today, electroencephalography occupied a major role in the measurement responsibilities of the anesthesiologist in 1960. The separation between cerebral hypoxemia and hypothermia was difficult, although it was clear in catastrophic cases that the electroencephalogram changed dramatically during the operation. An ear oximeter using infrared light was believed to be efficacious and was one of the earliest demonstrations of an effort toward noninvasive determination of the O_2 content of the arterialized blood during cardiopulmonary bypass. Monitoring was achieved with devices that had been adapted from the cardiac catheterization laboratory and recorders used both heated styluses and mirrored galvanometry and light-sensitive paper.

The conduct of cardiopulmonary bypass was of special interest because so many of the intraoperative and postoperative problems appeared to be associated with its use. Two general types of oxygenators were used: the screen (Gibbon) or the disc (Kay-Cross). Each required priming with large volumes of whole blood.[3–7]

Blood volume requirements for cardiac surgery caused enormous concern, and this led to a series of experiments and determinations by many centers of circulating blood volume by use of I-131 and chrominum-51 before, during and after cardiopulmonary bypass. The problems, in great part, could be traced to the fact that the extracorporeal circuit had a volume that was equal to or greater than the patient. Hemodilution with crystalloid prime was not thought possible with the devices in use until the laboratory work of Neptune et al demonstrated efficacy.[3] These data from dogs and patients were not accepted readily by the clinical community for several years.

The immediate postoperative interval was the most difficult for anesthesiologists, cardiac surgeons and intensive care unit nurses. It was quickly learned that volume-controlled ventilators were necessary and that a major characteristic of the immediate postoperative interval was an alveolar-capillary block, which was related to a phenomenon of water and protein extravasation into the pulmonary interstitium. This was later traced to the large volumes of unfiltered blood and crystaloid given in the prime and during the procedure. Although most heart-lung machines had arterial

line filters, the pore size was large. The quantity and size of the solid microemboli in the stored blood and the perfusate were not appreciated.

Postoperatively, low cardiac output was common. Whether or not the use of Melrose's solution[4] was responsible or the use of anoxic arrest was the cause were not answered in the symposium. Improved methods of protection of the heart were clearly needed, and either method was hazardous allowing precious few minutes for repair of complex lesions. The agent of choice for poor contractility was digitalis in the form of ovabain because of its rapid onset of action.

Arrhythmia was a major problem with the early advent of closed- and open-heart surgery. Most arrhythmias were believed to be a result of inadequate oxygenation and carbon dioxide accumulation or were secondary to hypotention from blood loss or anesthetic agents. All reports emphasized that the minimal amount of anesthesia must be given and that careful attention to hyperventilation and avoidance of metabolic acidosis was mandatory. An arterial pH >7.45 was recommended regardless of temperature, and this was primarily done through hyperventilation, which was the hallmark of the management of early anesthesia.

The era of open-heart surgery was just beginning. The Los Angeles group reported that anesthesia had been given over a 4-year interval to 164 patients who had undergone cardiac operation with the use of cardiopulmonary bypass and hypothermia and general anesthesia was given to 68 patients for the performance of a cardiac procedure.[5] At that time, most patients (548) were anesthetized for cardiac catheterization.

Of historical interest was the report from Cleveland in which 429 consecutive cardiac surgical patients had a hospital mortality rate for the Beck I operation of 6% over a 5-year interval, the last 200 patients having a 2% hospital mortality rate.[6] This operation consisted of abrasion of the pericardium by mechanical means and application of trichloracetic acid and powdered asbestos. Additionally, a suture, placed from the external surface of the heart, surrounded the coronary sinus, narrowing it to approximately 3 mm. The theory was that the resulting congestion increased coronary sinus pressure, which would stimulate the development of intercoronary anastomoses within the ischemic myocardium. These operations were done through a left lateral thoracotomy without cardiopulmonary bypass and were followed by intercostal blockade with tetracaine.

The remaining one-third of the reports covered a variety of topics. One involved the problem of heart failure, which occurred in the immediate postpartum interval and was found to be related to the presence of heart disease in practically all patients. Another involved the relation between the cerebral circulation and arrhythmia, and Corday and Irving[7] reported that there was an intimate relation between the two. The cerebral circulation was also studied by Wolfe,[8] in Cleveland, who attempted to simulate the clinical situation of ventricular fibrillation under 2 conditions, normothermia and mild hypothermia (31°C). Even mild hypothermia provided protection against cerebral damage. An anecdotal article of historical note involved the notes by Thomas Bevel Peacock on dissecting aneurysm as he had observed it in 1843. He reported 5 cases to which he appended 14 from the published reports and attempted to develop a theory of pathogenesis and life history.

A variety of case reports followed. One involved congenital tricuspid stenosis, indeed a rarity both then and now. An aneurysm of the right coronary artery was described with rupture into the right atrium, with 1-year survival. Additionally, the problem of neonatal digitalis intoxication through the placenta was described in a mother requiring this compound. Wenckebach's phenomenon associated with hyperparathyroidism and the problem of the atypical patent ductus arteriosis were reviewed. The October issue contained the abstracts from the Ballisticardiographic Research Societies. In the President's column, the educational mission of The American College of Cardiology was emphasized. At that time, the college's annual meeting was held jointly with the American Heart Association. The ninth interim meeting of the American College of Cardiology's program was printed, and most prominent among these were so-called firestone conferences, which covered an enormous range of topics.

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FROM THE EDITOR

Mitral Valve Prolapse and Systemic Hypertension

In the USA there are approximately 160 million persons over 20 years of age (total population = 238 million). Of the 160 million, an estimated 8 million (5%) have auscultatory evidence of mitral valve prolapse (MVP) and 60 million (37%) have systemic hypertension (SH) (arterial pressure $\geq$140/90 mm Hg). Accordingly, of the 8 million with MVP, nearly 3 million (0.37 $\times$ 8) have SH, and of the 60 million with SH, 3 million (0.05 $\times$ 60) have MVP. The number of persons, therefore, with both MVP and SH in the USA is substantial.

Except in the person with left ventricular outflow obstruction, the systemic peak systolic arterial pressure is identical to the left ventricular peak systolic pressure, which of course is the pressure that closes the mitral valve orifice during ventricular systole. The normal mitral valve withstands elevation of the left ventricular peak systolic pressure without development of mitral regurgitation unless mitral anular calcific deposition is heavy, a process which is more frequent in hypertensive than in normotensive persons.[1] But how well does the defective, i.e., prolapsed or floppy, mitral valve tolerate chronic elevation of the left ventricular peak systolic pressure? My answer is "poorly," and the reason is because the associated SH (specifically, the elevated left ventricular systolic pressure) greatly increases the frequency of spontaneous rupture of mitral chordae tendineae, an occurrence virtually limited to patients with preexisting MVP. Jeresaty and associates[2] found underlying MVP in 23 (92%) of 25 patients with spontaneous rupture of mitral chordae tendineae and Hickey and associates[3] found underlying MVP in 29 (94%) of 31 patients with spontaneous rupture of mitral chordae tendineae. In an earlier study,[4] my colleagues and I examined 60 operatively excised purely regurgitant prolapsed mitral valves: 13 had ruptured chordae tendineae and of these, 11 (85%) had had SH before valve replacement; of the remaining 47 valves, none had ruptured chordae tendineae and only 11 (23%) of them had had SH preoperatively.

The normal mitral leaflets, as with the leaflets of all 4 cardiac valves, consist of 2 components: the fibrosa and the spongiosa. The fibrosa consists of collagen fibrils and the spongiosa, of an acid mucopolysaccharide material. In MVP the collagen fibrils of both the leaflets and chordae tendineae are defective[5] and probably, at least initially, decreased in number, and the spongiosa material, the "weaker" of the 2 components, is present in excessive amounts. It is reasonable to believe that the weaker the mitral leaflet and chordal structures, the greater the effect on them of the left ventricular systolic pressure, and the greater the mitral closing pressure the greater its effect on the defective mitral leaflet and chordal structures.

In summary, the normal mitral valve tolerates elevated left ventricular systolic pressures (mitral closing pressures) well, i.e., without creating mitral regurgitation and without rupturing mitral chordae tendineae. The prolapsed mitral valve, in contrast, contains defective collagen fibrils and excess spongiosa and it appears to withstand elevated left ventricular systolic pressures poorly as manifested by a high frequency of spontaneous rupture of chordae tendineae (and probably also by an increased degree of leaflet prolapse). Thus, proper treatment of SH may prevent or delay the appearance of severe mitral regurgitation that occurs in some patients with MVP.

William C. Roberts

William C. Roberts, MD
Editor in Chief

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LETTERS*

RELATION BETWEEN ELECTROCARDIOGRAPHIC AND SCINTIGRAPHIC LOCATION OF MYOCARDIAL ISCHEMIA IN 1-VESSEL CORONARY ARTERY DISEASE

In the report of Fox et al[1], the investigators claimed that no studies had satisfactorily addressed the problem of whether the exercise electrocardiogram (ECG) can locate the site of ischemia, and quoted our recent article.[2] Apart from minor methodologic differences in exercise testing and analysis of thallium scans, the protocol used by Fox et al. was identical to our own. The same criteria for patient selection were used, i.e., only patients with 1-vessel coronary artery disease (CAD), interpretable ECGs and no previous myocardial infarction were included, and an independent method (thallium scan) was used to document and locate ischemia. The only difference between the 2 studies was that 18% (not 25% as quoted by Fox et al) of our patients with 1-vessel CAD had normal thallium scans, whereas all patients in the study of Fox et al had reversible defects. It is well known that the thallium scan does not have 100% sensitivity in detecting patients with 1-vessel CAD as was reported in a previous study from the same group.[3] Certainly, the exclusion of patients without thallium defects confers no unique advantage on the study as claimed by Fox et al. We were nevertheless pleased that Fox et al confirmed our finding that ST-segment depression on the 12-lead exercise ECG did not predict the anatomic site of ischemia.

S. B. Freedman, MB, Phd
R. F. Dunn, MB
Sydney, Australia
22 October 1984

1. **Fox RM, Hakkil AH, Iskandrian AS.** Relation between electrocardiographic and scintigraphic location of myocardial ischemia during exercise in 1-vessel coronary artery disease. Am J cardiol 1984;53:1529–1531.
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3. **Iskandrian AS, Lichtenberg R, Segal BL, Mintz GS, Mundth ED, Hakki AH, Kimbiris D, Bemis CE, Croll MN, Kane SA.** Assessment of jeopardized myocardium in patients with 1-vessel disease. Circulation 1982;65: 242–247.

* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

BUCINDOLOL

We were interested in the recent study by Rotmensch et al (Am J Cardiol 1984;54: 353–356). We also had experience with bucindolol in 8 patients. The duration of action of bucindolol may not be as long as proposed by Rotmensch et al, because we observed significant changes in blood pressure 1 hour after a 150-mg dose was administered, which was not seen 10 hours later (Table I). Doses of bucindolol <150 mg produced less antihypertensive response suggesting that 150 mg is an effective dose. We also can confirm the partial intrinsic sympathomimetic action of bucindolol because there was a dose-related inhibition of exercise-induced tachycardia, whereas the pulse rate at rest remained unchanged.

It also has been suggested that bucindolol may have another beneficial action, α-blocking activity. This α-receptor blockade would theoretically offset some of the β-receptor-induced bronchoconstriction in the lung. We previously demonstrated that labetolol (an α-β-receptor blocker) produced bronchoconstriction of a similar degree to the most cardioselective β-receptor blocker, atenolol.[1] Bucindolol in our study produced no effect on peak flow FEV_1 and FVC in our study suggesting that it may be as safe as the more selective β blockers. One small point of caution: We observed increases in the skeletal creatine kinase in 3 patients, which normalized in 2 on cessation of therapy. In 1 patient, elevated creatinine kinase has persisted for 1 year. Increases in creatine kinase have been reported with other β blockers possessing intrinsic sympathomimetic action,[2] but we believe that careful observation is necessary.

J. S. Gill, MD
D. G. Beevers, MD
Birmingham England
29 October 1984

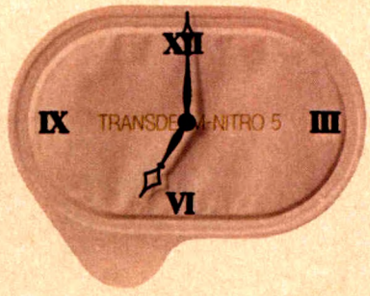
1. **Jackson SHD, Beevers DG.** Comparison of the effects of a single dose of atenolol and labetolol on airways obstruction in patients with hypertension and asthma. Br J Clin Pharmacol 1983;15:553–556.
2. **Saruta T, Suzuki H, Nakane H, Kondo K, Ito H.** Changes in CPK and its isoenzymes in the treatment by beta-blocking agents. Abstract 771 in Abstracts of the 10th scientific meeting of the International Society of Hypertension, Interlaken 1984.

SERIAL ELECTROPHYSIOLOGIC TESTING AFTER ACUTE MYOCARDIAL INFARCTION

Long-term reproducibility of recurrent sustained ventricular tachycardia (VT) by programmed electrical stimulation is taken as a priori by many electrophysiologists. Therefore, the report by Schoenfeld et al[1] is a welcomed confirmation of the anecdotal experiences of others. We reported our anecdotal experiences in 2 recent case reports.[2,3] Unlike Schoenfeld et al, our focus has been to address the long-term reproducibility of sustained VT shortly after acute myocardial infarction (AMI). There is evidence that patients with complex ventricular arrhythmias, occurring in the recovery phase of AMI are at an increased risk for sudden death in the first year. Because many of these high-risk patients do not die in the succeeding year, one might conclude that their early electrical instability may have changed with time. Our first report[2] addressed the concept that induced sustained VT in a patient early after AMI may not be replicated at 20 months. This patient was well 4 years after AMI. In our second study (Luck et al[3]), we reproduced sustained VT on 5 occasions after an anterior AMI in a high-risk patient over a 15-month period. This second patient has never had spontaneous sustained VT and remains asymptomatic without antiarrhythmic therapy 3 years after AMI. We believe that long-term reproducibility of VT by electrical stimulation may be more important in patients with sustained VT after AMI. If arrhythmias are not inducible after 1 to 2 years, then the prognosis may clearly be different. Likewise, empirical therapy or therapy with programmed electrical stimulation after AMI may be discontinued after 1 to 2 years if a repeat study reveals negative results.

Jerry C. Luck, MD
Christopher R.C. Wyndham, MD
Houston, Texas
29 October 1984

1. **Schoenfeld MH, McGovern B, Garan H, Ruskin JN.** Long-time reproducibility of responses to programmed cardiac stimulation in spontaneous ventricular tachyarrhythmias. Am J Cardiol 1984;54:564–569.
2. **Pratt CM, Seals AA, Luck JC.** The clinical significance of ventricular arrhythmias after myocardial infarction. Cardiol Clin 1984;2:3–11.
3. **Luck JC, Wyndham CRC, Mann DE, Batty JW, Herre JM, Griffin JC.** Serial electrophysiologic testing with a permanent pacemaker after acute myocardial infarction. Pace 1984;7:663–667.



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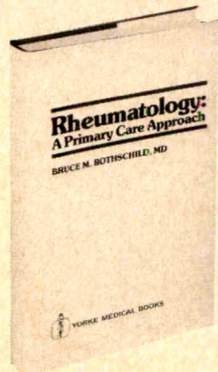

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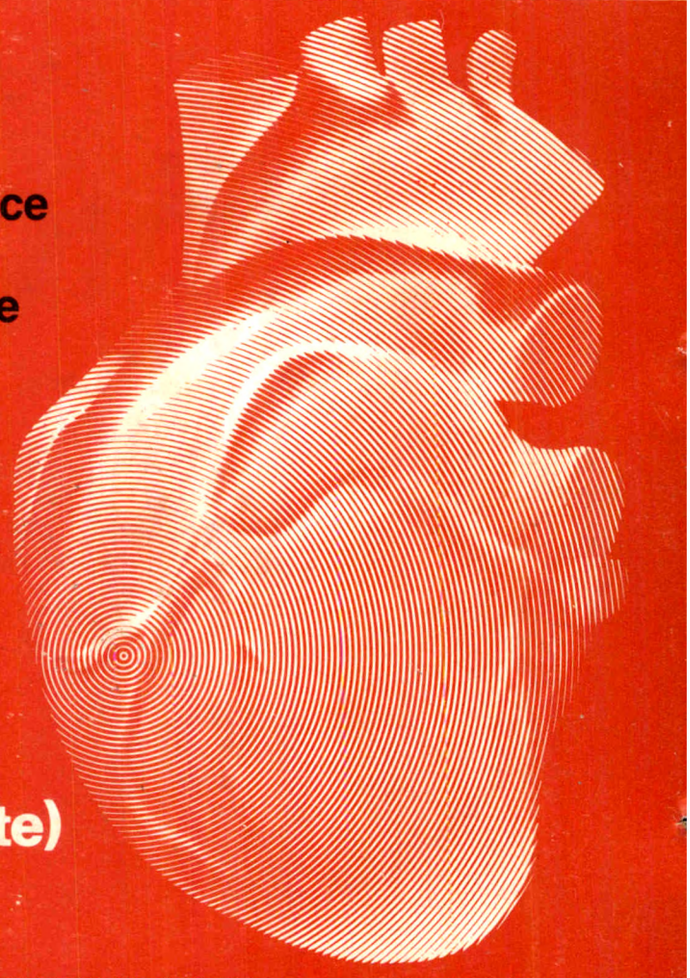

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Editor:
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A Symposium: Esmolol—An Ultrashort-Acting Intravenous Beta Blocker

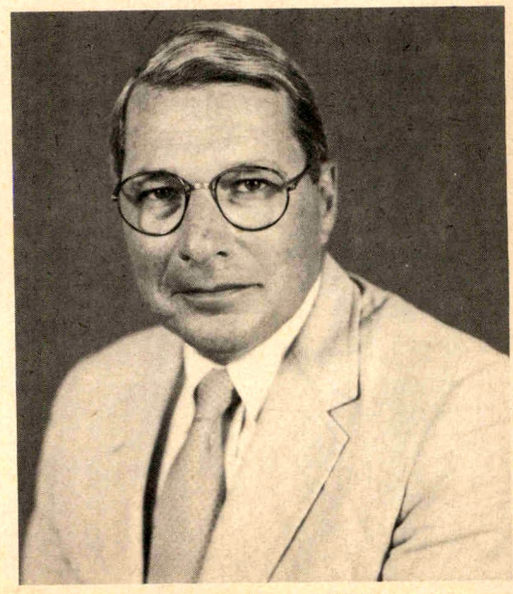
Introduction

EDMUND H. SONNENBLICK, MD

Beta-adrenergic stimulation with resultant tachycardia, systemic hypertension and arrhythmia may produce adverse consequences in many acute settings, and long-term control of these effects by β-adrenergic blockade is well established. In ischemia, reduction of heart rate, contractility and blood pressure reduces myocardial oxygen consumption, while the prolonged duration of diastole, which occurs with a slower heart rate, enhances diastolic coronary blood flow. For these reasons, β-adrenergic blocking agents have been effective not only in the treatment of chronic ischemia (angina), but also in aborting impending myocardial infarction with unstable angina and intermediate syndromes. Reduction of the extent of myocardial infarction, once the process has advanced beyond reversible ischemia, is much less clear. Thus, β-adrenergic blocking agents have much to offer therapeutically in early ischemia. However, the prolonged action of available β blockers complicates their use in acute settings because withdrawal of sympathetic tone when extensive myocardial necrosis may have already occurred and impending failure has ensued could be detrimental. Moreover, bronchospasm or conduction defects may occur idiosyncratically. Thus, the availability of a β-blocking agent such as esmolol, whose action is rapid in onset, can be titrated and very rapidly terminated when required, would provide an important safety factor in these settings while testing and treating the acute problem. The same applies for use of such an agent to treat rapid supraventricular tachycardias.

This symposium was held to review the information available on esmolol. It begins with an overview of the basic pharmacology by Dr. Gorczynski, who concludes that esmolol is a cardioselective β blocker with minimal partial agonist activity or membrane depressant properties and has a half-life of approximately 9 minutes.

Dr. Lowenthal describes the clinical pharmacology, pharmacodynamics and drug interaction studies with esmolol. He confirms the pharmacologic profile of esmolol in humans and reports no clinically important effects on vital signs, blood chemistry, hematology or drug interactions. The clinical electrophysiology of esmolol is described by Dr. Greenspan as typical of, and



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of comparable intensity to, other β blockers. Its unique advantage is its rapid onset and reversal of electrophysiologic effects, making it particularly suited for acute antiarrhythmic intervention in clinical situations in which the risk of untoward effects of β blockade is high. Hemodynamic studies by Dr. Iskandrian, who used noninvasive techniques, demonstrate typical β-adrenergic blocking effects with esmolol. Because the efficacy of esmolol in supraventricular tachycardia has been established, Dr. Morganroth undertook a study to compare esmolol to propranolol for treatment of supraventricular tachycardia. He concludes that esmolol, because of its short half-life and efficacy equal to propranolol, has marked advantages in the control of supraventricular tachyarrhythmia in patients in the intensive care unit.

Drs. Kloner, Kirschenbaum and colleagues describe the results of the only study to date of esmolol in patients with acute ischemia or infarction. They conclude that esmolol is safe and effective in lowering heart rate and arterial pressure (and, hence, rate-pressure product) in patients with acute myocardial ischemia and infarction and that hemodynamic effects are rapidly reversed after termination of the infusion. In patients with acute ischemia in whom oxygen demand should be reduced, but in whom β blockade may precipitate heart failure, bronchospasm, conduction abnormalities or hypotension, esmolol may be safer to use than conventional longer-acting β blockers.

In another acute, intensive care setting Dr. Gray compared the effects of esmolol and nitroprusside in postoperative hypertension in a crossover study. For hypertension early after cardiac surgery, he concludes that esmolol is safe, effective and rapid in onset, and when compared with nitroprusside, results in less unwanted decrease in diastolic blood pressure and oxygen saturation. In addition, heart rate and cardiac index are decreased with esmolol, as one anticipates from the use of β-adrenergic blocking agents in general.

Another potential clinical application of esmolol is in the control of perioperative tachycardia and hypertension in surgical patients at high risk of cardiac ischemia. This was studied by Dr. Reves, who believes that its rapid onset and elimination make esmolol particularly well suited for preventing and treating the adrenergic responses to intraoperative stresses, which may be very intense but are often brief.

This early experience with esmolol suggests that it will provide an important option to therapy in acute clinical settings. We look forward eagerly to the results of ongoing studies in acute ischemic settings as well as other indications for the use of esmolol.

Basic Pharmacology of Esmolol

RICHARD J. GORCZYNSKI, PhD

Preclinical studies show that esmolol is an ultrashort-acting, cardioselective β blocker that possesses minimal partial agonist action or membrane-depressant properties. The electrophysiologic and hemodynamic actions of esmolol are the result of β blockade. No direct, β receptor-independent cardiovascular actions have been identified with β-blocking doses in laboratory experiments. Because esmolol slows atrioventricular conduction, increases atrioventricular refractoriness and decreases the determinants of myocardial oxygen demand, it should have use in the treatment of supraventricular tachycardias and acute myocardial ischemia. Esmolol, because of its ultrashort duration of action, should be safe for the induction of β blockade in patients who are critically ill and is ideally suited for rapidly changing levels of β blockade in this clinical situation.

(Am J Cardiol 1985;56:3F–13F)

Beta blockade has become a well-accepted treatment for various cardiovascular diseases, including supraventricular tachyarrhythmias, hypertension and angina pectoris.[1,2] Recently β blockade has been shown to decrease the long-term mortality rate of survivors of acute myocardial infarction.[3,4] Although use of β blockade in reducing ischemic damage and incidence of primary ventricular fibrillation during the acute phase of myocardial infarction has been supported by several recent clinical trials,[5–7] the efficacy of β blockers in this setting has not been proved[8,9] and necessarily depends on how soon after the onset of symptoms therapy can be instituted.

The efficacy of β blockers in the treatment of supraventricular tachyarrhythmias hinges on their well-known effect of slowing conduction through, and of increasing the refractoriness of, the atrioventricular (AV) node. These actions are primarily a result of inhibition of sympathetic influences via blockade of β receptors.[10]

It is generally accepted that some degree of sympathetic activation accompanies acute ischemic insults to the heart as a result of either physiologic or psychologic stimuli or both.[11,12] Moreover, ample evidence shows that in the presence of a defect in oxygen delivery to the myocardium, increases in sympathetic tone can initiate ischemia, infarction and arrhythmia by producing an increase in myocardial oxygen demand and perhaps in some instances by further reducing myocardial oxygen supply. Because the deleterious effects of sympathetic activity on the heart are mediated primarily via β-adrenergic receptors, β blockade can lessen the severity of ischemia by reducing the heart's oxygen need and, possibly, by augmenting myocardial oxygen supply.[2,13]

What is far from clear, however, is the degree to which sympathetic support of the normal areas of the heart compensates for local dysfunction of hypoperfused areas. Although this undoubtedly occurs in acute myocardial ischemia, the degree to which cardiac function is dependent on the sympathetic nervous system is usually unknown at the time of therapy and, therefore, the hemodynamic effects of β blockade in this setting are difficult to predict. Thus, the possibility of inducing cardiac failure is always a risk.[2,14] A related concern is the risk associated with the use of β blockers in patients with coronary artery disease during anesthesia to blunt the tachycardia and hypertension response to general surgical stimuli. These responses can provoke myocardial ischemia and infarction in such patients during surgery.[15,16] Although β blockers can control the phenomenon, the presence of β blockade may become problematic during either surgery or the postoperative recovery period, when cardiac function is usually decreased.[17]

In 1982, Zaroslinski et al[18] described the concept of ultrashort-acting β-adrenergic blockers; they envisioned a compound that is extensively and rapidly metabolized to inactive products much the same as catecholamines or nitroglycerin. Such a short-acting compound could then be administered by constant intravenous infusion to provide for controlled levels of β blockade that could be titrated and rapidly altered if

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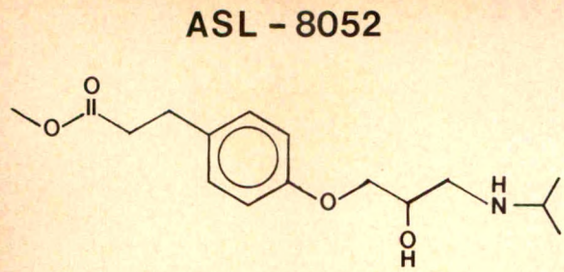

FIGURE 1. Molecular structure of esmolol (ASL-8052).

required. An ultrashort-acting β blocker was expected to be a much safer type of β blocker to use in critical care situations in which β-blocker therapy is required, such as unstable angina, acute myocardial infarction, and surgically induced tachycardia, tachyarrhythmias and hypertension. If deleterious hemodynamic effects or cardiac failure occurred as a result of β blockade with an ultrashort-acting β blocker, rapid recovery of function could be attained within minutes by simply reducing the infusion rate or ceasing administration completely.

Recent reports have outlined the molecular approaches to the design and development of ultrashort-acting β blockers.[19–22] From this work, esmolol, which is a cardioselective β blocker that possesses an extremely short duration of action, was subsequently identified[19] and characterized.[18,23–25]

Beta-Blocking Potency and Duration of Action

Esmolol (ASL-8052) (Fig. 1) is a phenoxypropanolamine, a molecular structure characteristic of conventional, second-generation β blockers. Also, esmolol contains an ester functionality in the para-position of the phenyl-ring. The presence and location of this ester are of fundamental importance in the determination of esmolol's cardioselectivity as well as its ultrashort duration of action.[19]

In initial in vitro experiments (Fig. 2), esmolol caused parallel, rightward shifts in isoproterenol concentration-response curves in guinea pig right atria and trachea.[23] The degree of rightward shift was concentration-dependent and the antagonism was always fully surmountable given sufficiently high doses of agonist. The Schild plots illustrated in Figure 3 indicate the linear relation between the concentration of esmolol and the degree of rightward shift in both tissues. The slopes of these relations did not differ significantly from 1, indicating that esmolol is indeed a β-receptor antagonist. In atria esmolol had a pA_2 of 7.0 indicating that it is about 30-fold less potent than propranolol, and about equipotent to metoprolol in this tissue. These data also indicate that esmolol was approximately 43-fold more potent at β receptors in atria than in trachea (pA_2 = 5.3).

The duration of action of esmolol was determined in barbiturate-anesthetized dogs.[23] The tachycardia and hypotension responses to a submaximal bolus dose of isoproterenol were measured before and at 10-minute intervals during and after 3 hours of continuous infusion of esmolol at different doses. Identical experiments were performed with propranolol for comparison. Esmolol caused a dose-dependent decrease in tachycardia responses. Steady-state levels of β blockade were achieved within 10 to 20 minutes of each infusion (Fig. 4). In contrast, blockade with propranolol progressively increased throughout most of the infusion period. The dose of esmolol that produced 50%

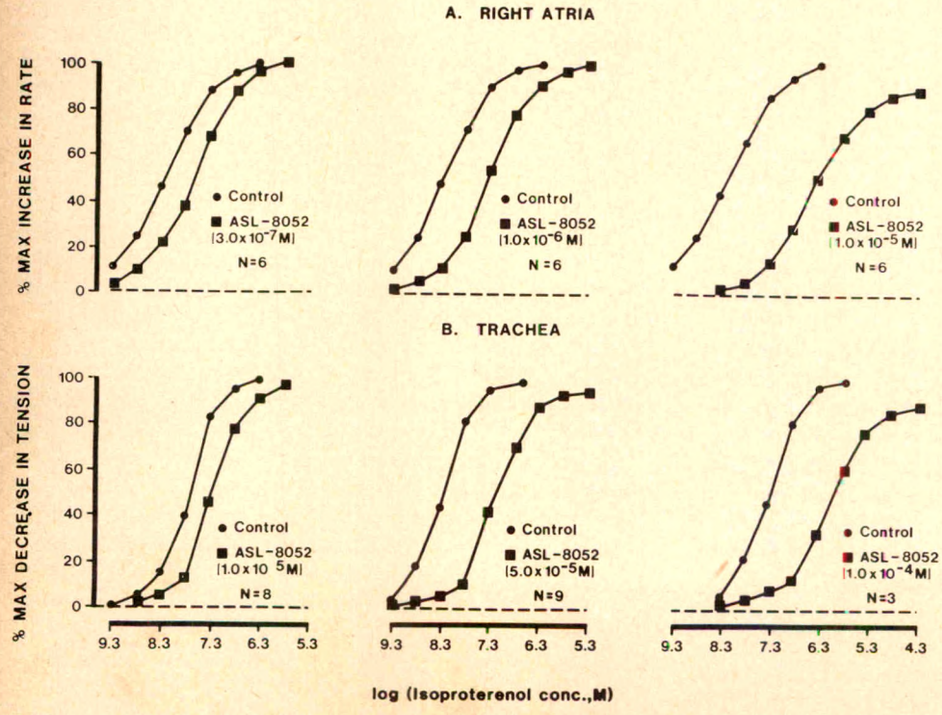

FIGURE 2. Isoproterenol concentration-response curves in **A,** isolated guinea pig right atria and **B,** trachea, in the absence and the presence of 3 concentrations of esmolol in separate experiments.

inhibition of the tachycardia response to isoproterenol was 50 μg/kg/min. After termination of the esmolol infusion, β blockade rapidly and dramatically decreased such that 20 minutes after esmolol no significant β blockade was detectable regardless of dose. This was in direct contrast to results obtained with propranolol, which indicated only minimal recovery from β blockade during the postinfusion observation period (up to 1 hour). Subsequent studies in conscious dogs, rabbits, rats and humans have confirmed that esmolol has a very short duration of action regardless of the species in which it is studied.

Although esmolol caused dose-dependent blockade of isoproterenol-induced tachycardia, it had no significant blocking effect on the hypotensive responses to isoproterenol (Fig. 5). This was in contrast to a rather dramatic blockade of isoproterenol-induced hypotension caused by propranolol. Thus, the cardioselective nature of β blockade with esmolol was clearly in evidence in this study.

The cardioselectivity of esmolol observed in vitro was further investigated in vivo using a constant flow perfused hindlimb preparation in pentobarbital-anesthetized, ganglion-blocked dogs.[13] Tachycardia and hindlimb vasodilator responses to a submaximal dose of isoproterenol were measured before and during continuous intravenous infusion of esmolol at doses that were increased at 10-minute intervals. Similar experiments were conducted with metoprolol and propranolol for comparative purposes. Esmolol caused dose-dependent blockade of isoproterenol-induced tachycardia, but produced only minimal blockade of isoproterenol-induced vasodilation (Fig. 6). These results were similar to those obtained with metoprolol, a cardioselective β blocker, but were different from those obtained with propranolol, which produced nonselective β blockade. When the effects of larger doses of esmolol were examined, blockade of vascular β receptors occurred, but equivalent levels of vascular β blockade required a dose of esmolol that was 100-fold greater than that required for cardiac β blockade. These data, therefore, confirm and extend in vitro data that initially suggested that esmolol was a cardioselective β blocker.

Ancillary Properties

Esmolol produced slight (<10%) increases in the rate of contraction of guinea pig right atria isolated from catecholamine-depleted animals at concentrations of 10^{-9} to 10^{-5} *M* (Fig. 7).[23] The compound produced a concentration-dependent depression in atrial rate at concentrations $>10^{-4}$ *M*. Esmolol had no effect on developed tension of left atria isolated from reserpinized guinea pigs at concentrations $\leq 10^{-5}$ *M*. Concentration-dependent depression in force was observed at higher concentrations.

Thus, only minimal partial agonist action was observed in isolated atria; in contrast, direct cardiac de-

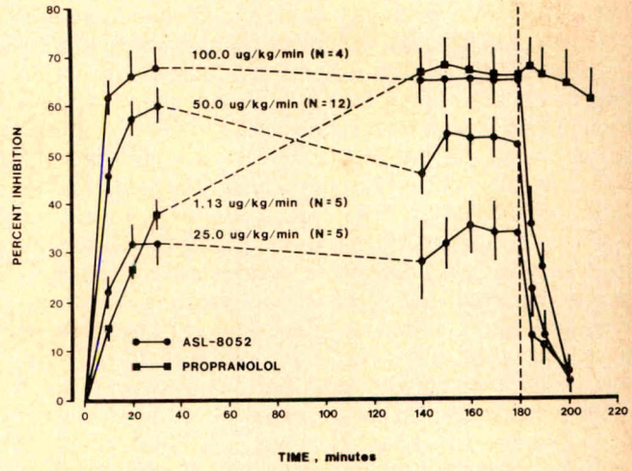

FIGURE 4. Percent inhibition of isoproterenol-induced tachycardia throughout a 3-hour constant intravenous infusion of esmolol (3 infusion rates) and propranolol, and recovery from β blockade after termination of β-blocker infusion.

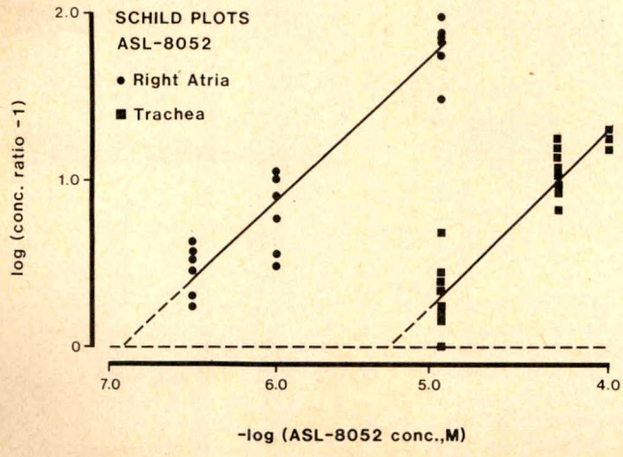

FIGURE 3. Schild plots obtained with esmolol in guinea pig right atria and trachea with isoproterenol as agonist.

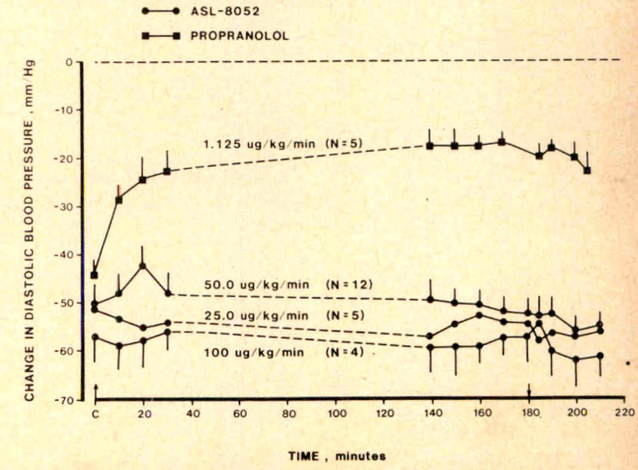

FIGURE 5. Isoproterenol-induced decreases in diastolic arterial pressure before, during and after a 3-hour constant intravenous infusion of esmolol (3 infusion rates) and propranolol. C = control response to isoproterenol in the absence of esmolol or propranolol.

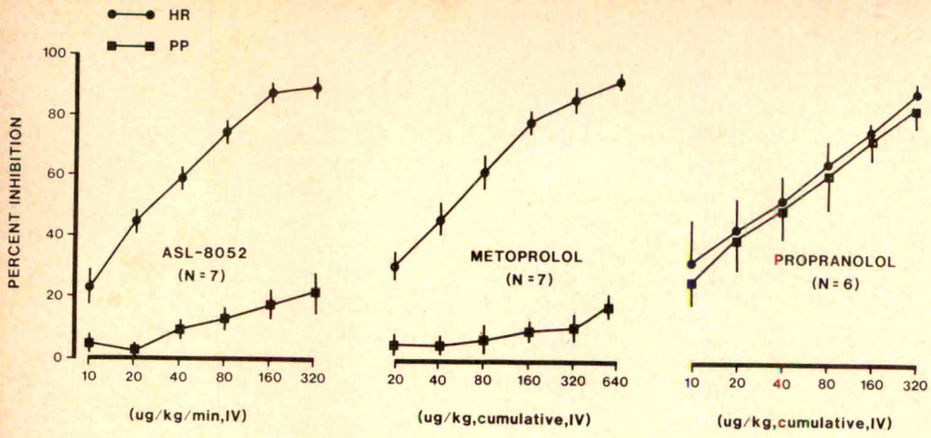

FIGURE 6. Percent inhibition of isoproterenol-induced increases in heart rate (HR) and decreases in hindlimb perfusion pressure (PP) in ganglion-blocked dogs with esmolol (**left**), metoprolol (**middle**) and propranolol (**right**), plotted as function of dose.

pression, which is a measure of myocardial membrane depression, occurred only at very high concentrations with esmolol. This latter finding suggests that esmolol possesses only slight membrane-depressant action and this has been confirmed by other related studies. Esmolol had no effect on conduction in the frog sciatic nerve at concentrations ≥ 0.1 *M* and did not affect corneal sensitivity in conscious rabbits at similar concentrations.

To examine further the direct effects of esmolol on cardiac tissue, studies were conducted in catecholamine-depleted, anesthetized dogs pretreated with reserpine.[24] Esmolol had no effect on heart rate, arterial blood pressure, left ventricular (LV) dP/dt or right ventricular contractile force at an intravenous dose of ≤ 500 μg/kg/min. Higher doses produced dose-dependent decreases in heart rate, arterial blood pressure and contractility and increases in LV end-diastolic pressure (EDP). These effects are likely a result of direct membrane depression and are characteristic of high doses of many β blockers. Of particular interest, however, is that in contrast to long-acting β blockers, direct cardiac depression with esmolol is rapidly reversible, as shown in Figure 8. In the dog whose data are shown in this figure, esmolol was infused at ascending dosages of 300 to 3,800 μg/kg/min at 10-minute intervals. At the end of the highest infusion rate, mean arterial pressure was approximately 15 mm Hg, contractility was severely depressed and LVEDP was dramatically increased. Cardiovascular recovery began within 1 minute after termination of esmolol infusion; essentially complete recovery occurred in approximately 10 minutes. Thus, although direct cardiovascular depression can be seen at extremely large doses of esmolol that would never be used clinically, the ultrashort duration of action of the compound provides a reassuring margin of safety in the event of an overdose.

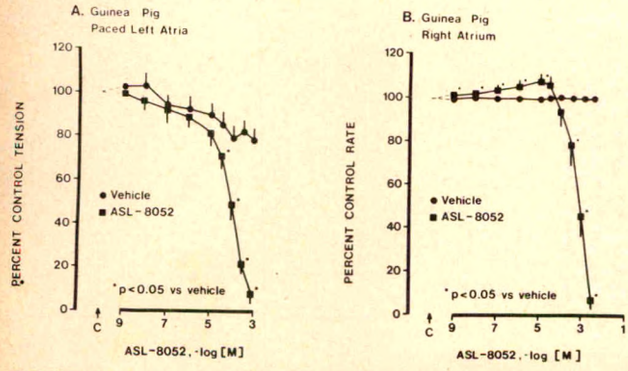

FIGURE 7. Direct effects of esmolol on developed tension of **A,** isolated paced guinea pig left atria and on spontaneous rate of contraction of **B,** isolated guinea pig right atria from reserpine-treated animals. **Arrow** indicates control values.

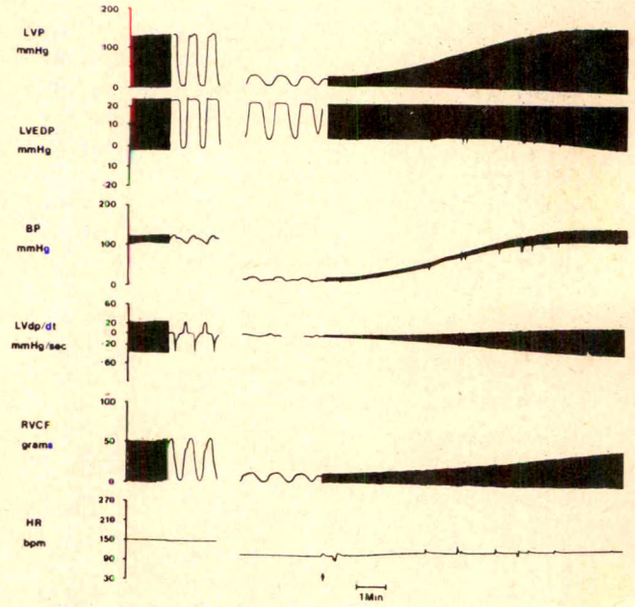

FIGURE 8. Original polygraph recording showing recovery of hemodynamic variables after high infusion rates of esmolol in a catecholamine-depleted, vagotomized dog. **Left,** predrug values. **Right,** to left of **arrow,** cardiovascular depression induced by large-dose rates of esmolol (3.8 μg/kg/min for 10 minutes). Infusion was terminated at **arrow**. BP = blood pressure; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVP = left ventricular pressure; RVCF = right ventricular contractile force.

Hemodynamic Effects of Esmolol

Brief intravenous infusions of esmolol (20 minutes) at doses of 5 to 160 μg/kg/min had no effect on arterial pressure, LVEDP, cardiac output, heart rate or peripheral vascular resistance in chronically instrumented, trained, conscious dogs (Figs. 9 and 10). Esmolol, however, produced a dose-dependent decrease in maximal LV dP/dt (23% at the largest dose), which fully recovered by 20 minutes after completion of the highest infusion rate of esmolol. Qualitatively similar effects were observed with short intravenous infusions of metoprolol and propranolol in the same experimental animals using doses that produced similar degrees of β blockade; however, propranolol and metoprolol in larger doses also decreased cardiac output and increased peripheral vascular resistance by about 30%. Propranolol also caused a small decrease in heart rate at larger doses.

In contrast to results with esmolol, however, the hemodynamic and electrocardiographic effects of metoprolol and propranolol were not diminished 20 minutes after administration of the largest dose. These data suggest that although esmolol lowered LV dP/dt in a dose-dependent fashion, as did propranolol and metoprolol, this effect did not influence cardiac output, whereas cardiac output decreased with the standard β blockers. Unlike propranolol and large doses of metoprolol, esmolol did not increase peripheral vascular resistance.

In pentobarbital-anesthetized, vagotomized dogs, esmolol produced more marked hemodynamic changes than were seen in conscious dogs.[24] Thus, esmolol (5 to 160 μg/kg/min) produced dose-dependent decreases in heart rate, LV dP/dt and right ventricular contractile force, which amounted to 15%, 35% and 35% reductions, respectively, with the largest dose tested. Esmolol also produced a very small decrease in diastolic blood pressure, which at maximum for this dose range averaged <10%. When autonomic tone was eliminated in these dogs by ganglion blockade, the same doses of esmolol did not significantly affect these variables.

The direct vascular effects of esmolol were examined in constant flow perfused hindlimbs of pentobarbital-anesthetized, ganglion-blocked dogs. Esmolol had no effect on hindlimb perfusion pressure at intravenous doses up to and including 1,280 μg/kg/min

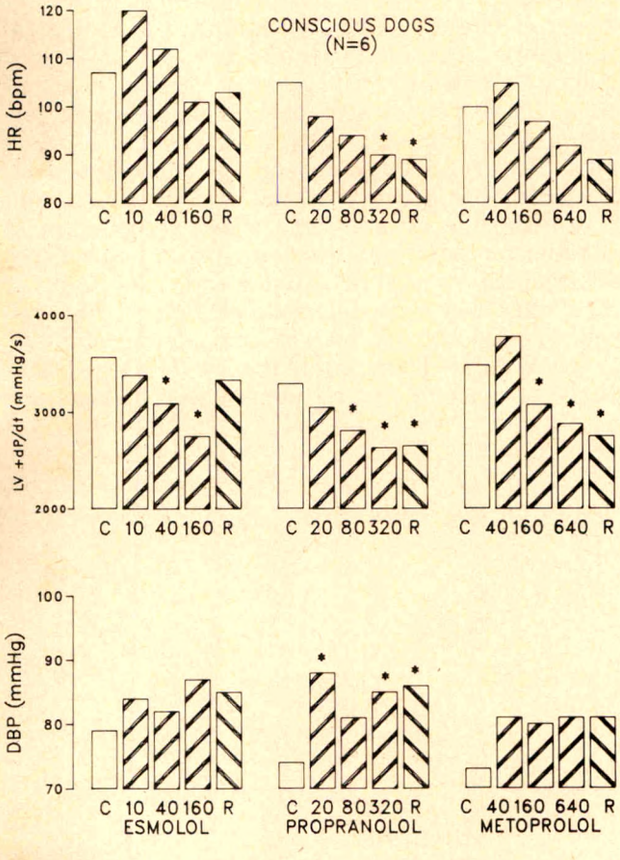

FIGURE 9. Hemodynamic effects of esmolol, propranolol and metoprolol in trained, chronically instrumented, conscious dogs. Number beneath columns refers to doses administered, expressed as μg/kg/min for esmolol and μg/kg, cumulative, for propranolol and metoprolol. * $p < 0.05$ vs control. C = predrug control value and R = value after 20 minutes of recovery, after infusion of each drug. DBP = diastolic blood pressure; HR = heart rate.

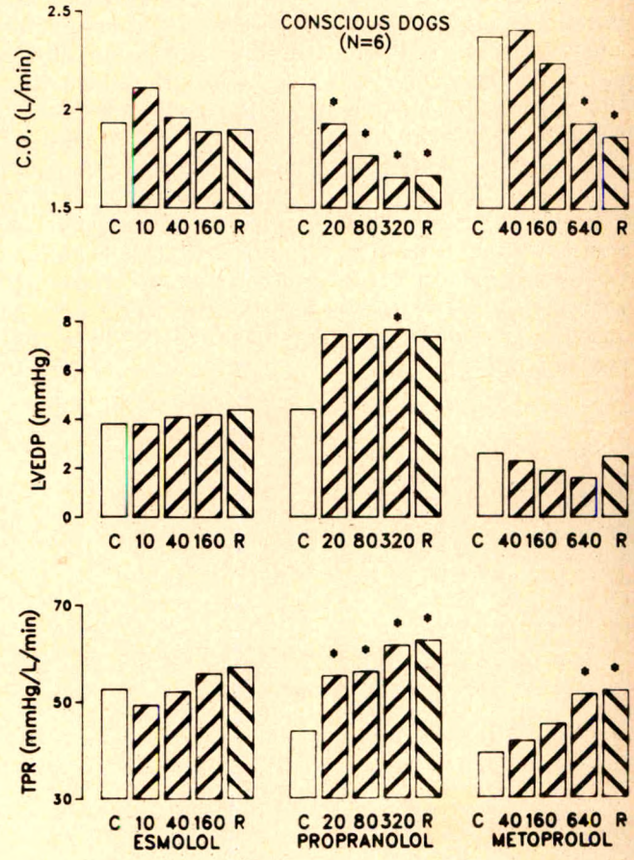

FIGURE 10. Hemodynamic effects of esmolol, propranolol and metoprolol in trained, chronically instrumented, conscious dogs under same conditions as described in Figure 9. * $p < 0.05$ vs control. CO = cardiac output; LVEDP = left ventricular end-diastolic pressure; TPR = total peripheral vascular resistance.

TABLE I Effect of Esmolol on Hindlimb Perfusion Pressure Responses to Norepinephrine in Ganglion-Blocked, Propranolol-Treated Dogs (n = 4)

Norepinephrine Dose (ng/kg, i.a.)	Hindlimb Perfusion Pressure (mm Hg)		
	28	56	112
Control	31 ± 8	40 ± 8	58 ± 9
Esmolol*			
100	31 ± 8	41 ± 8	59 ± 9
200	33 ± 8	44 ± 9	62 ± 9
400	35 ± 7	44 ± 9	62 ± 8

Data are mean ± standard error of the mean.
* In μg/g/min, intravenously.
i.a. = intraarterial.

(Fig. 11). It induced slight vasoconstriction upon close intraarterial infusion over the range of 45 to 360 μg/kg/min. The maximal increase in perfusion pressure observed with intraarterial dosing was 19 ± 6 mm Hg at a dose of 180 μg/kg/min. These results indicate that esmolol is devoid of direct vascular action at dosages that are within or above the β-blocking dosage range, but suggest that extremely large dosages may cause vasoconstriction.

To investigate the possibility that esmolol may possess some degree of α-adrenergic blocking action, hindlimb vasoconstriction responses to norepinephrine were examined before and during infusion of esmolol at increasing doses.[23] Esmolol did not modify the norepinephrine dose-response curve (Table I). Also, the drug did not modify hindlimb vasoconstrictor responses elicited by stimulation of the ipsilateral sympathetic chain (Fig. 12). In these studies in the neurally intact hindlimb, esmolol had a tendency to produce vasoconstriction, although this was not statistically significant. Thus, esmolol does not interfere with peripheral sympathetic nerve function, is not a vasodilator and does not produce α blockade in the canine hindlimb.

The effects of esmolol on cardiac hemodynamics, coronary blood flow and myocardial oxygen consumption were also studied.[24] Esmolol at 310 μg/kg/min produced significant decreases in heart rate and LV dP/dt but had no effect on arterial blood pressure or myocardial oxygen extraction (Fig. 13). Esmolol reduced myocardial oxygen consumption and slightly increased coronary vascular resistance. Esmolol also completely eliminated cardiostimulation in response to isoproterenol. These effects are well-known characteristics of β blockade and form the basis for the use of these agents for the treatment of ischemic heart disease.

Electrophysiologic effects of esmolol: The effects of esmolol on cardiac transmembrane potential were examined in vitro using a variety of different cardiac tissues and conventional microelectrode techniques. Esmolol had no effect on the frequency or character of spontaneous activity in the isolated rabbit sinus node, nor did it alter the action potentials of AV nodal cells at concentrations of $\leq 10^{-5}$ *M*.

The effects of norepinephrine on sinus rate and AV nodal conduction, however, were blocked by esmolol at concentrations of 10^{-7} to 10^{-5} *M*. The compound also blocked triggered activity induced by norepinephrine in canine atrial fibers within the same concentration range. In canine Purkinje fibers, esmolol at 10^{-7} and 10^{-6} *M* slightly increased resting membrane potential, perhaps indicative of the small degree of partial agonist activity previously observed in isolated atria. The drug had no effect on other measures of the Purkinje fiber action potential at concentrations of $\leq 10^{-5}$ *M*. Higher concentrations produced a decrease in action potential amplitude, maximum rate of depolarization and action potential duration indicative of membrane depression. Esmolol also blocked norepinephrine-induced automaticity and slow responses in canine Purkinje fibers within the lower concentration range. These results are characteristic of β blockers in

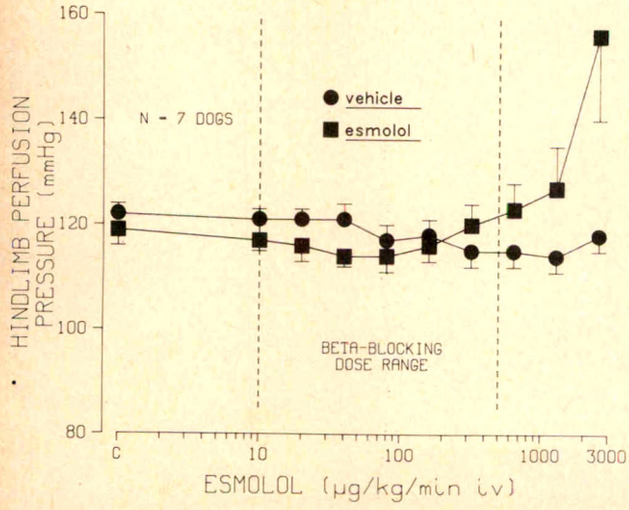

FIGURE 11. Direct effects of esmolol on vasculature of canine hindlimb, perfused at constant flow. Animals were vagotomized and pretreated with hexamethonium bromide to produce ganglion blockade before administration of esmolol.

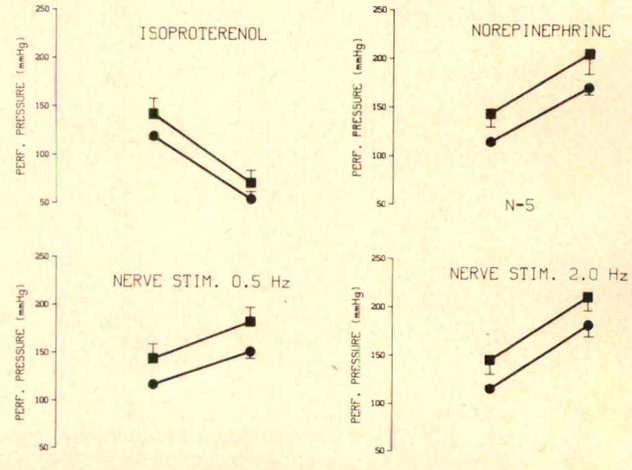

FIGURE 12. Lack of effect of esmolol (300 μg/kg/min) on perfusion pressure responses to isoproterenol, 10 ng/kg, intraarterially, norepinephrine, 100 ng/kg, intraarterially, and sympathetic chain stimulation in the constant flow-perfused canine hindlimb. ● = saline; ■ = esmolol.

TABLE II Effect of Esmolol on Sinus Node Recovery Time (SNRT), Conduction Intervals and AV Nodal Refractoriness in Anesthetized Dogs (n = 8)

	Control	Esmolol*	p
SNRT (ms)	416 ± 13	544 ± 19	<0.05
A-H (ms)	65 ± 6	86 ± 6	<0.05
H-V (ms)	33 ± 2	32 ± 2	
RRP (ms)	243 ± 6	268 ± 5	<0.05
FRP (ms)	226 ± 4	266 ± 8	<0.05
AVN-W (ms)	184 ± 9	233 ± 11	<0.05

* Esmolol infused intravenously at 310 μg/kg/min.
AVN-W = AV nodal-Wenckebach cycle length; FRP = functional recovery period; RRP = relative refractory period.

TABLE III Effect of Esmolol on the Incidence of Ventricular Fibrillation (VF) After Abrupt Coronary Artery Occlusion in Anesthetized Dogs

	Control (n = 6)	Esmolol (n = 6)	
No VF	2	6	p <0.05
VF	4	0	

general and indicate that esmolol lacks direct, pharmacologically significant electrophysiologic effects at reasonable β-blocking concentrations.

The effects of esmolol on intracardiac conduction in intact hearts was studied in pentobarbital-anesthetized, open-chest dogs instrumented for recording of right atrial, right ventricular and His bundle electrograms. Conduction intervals, sinus node recovery time and AV nodal refractory periods were measured before and during constant intravenous infusion of esmolol at 310 μg/kg/min. The AV nodal Wenckebach cycle length was also determined during incremental atrial pacing. At the basic cycle length of 300 ms, esmolol significantly lengthened the sinus node recovery time and the A-H conduction interval (Table II). The H-V interval, however, was not affected by the drug. These changes were also associated with significant increases in the relative and functional refractory periods and AV nodal Wenckebach cycle length during esmolol infusion. These observations are characteristic of β blockers and form the basis for their use in controlling elevated ventricular rate resulting from supraventricular tachycardia or for interruption of reentrant pathways involving the AV node. Esmolol-induced slowing of AV conduction and increased AV refractoriness are likely a result of inhibition of sympathetic tone in these animals, because in vitro the drug had no direct effect on the AV node at β-blocking concentrations.

Effects of esmolol on manifestations of myocardial ischemia: Intravenous infusion of esmolol at 150 μg/kg/min in anesthetized dogs decreased the incidence of spontaneous ventricular fibrillation induced by abrupt occlusion of the left anterior descending and anterior septal coronary arteries (Table III). In this study, esmolol decreased heart rate but had no significant effect on mean arterial blood pressure.

Pharmacodynamics and pharmacokinetics of esmolol: Because the concept of ultrashort-acting β blockers reflects a pharmacokinetic departure from conventional agents and because the primary use of an ultrashort-acting β blocker is to enable titratable β blockade, the pharmacokinetic and pharmacodynamic characteristics of esmolol are of singular importance. These properties were characterized in anesthetized dogs in which blood levels of esmolol were determined by either gas chromatographic methods or use of carbon-14-labeled compound. Both methods require im-

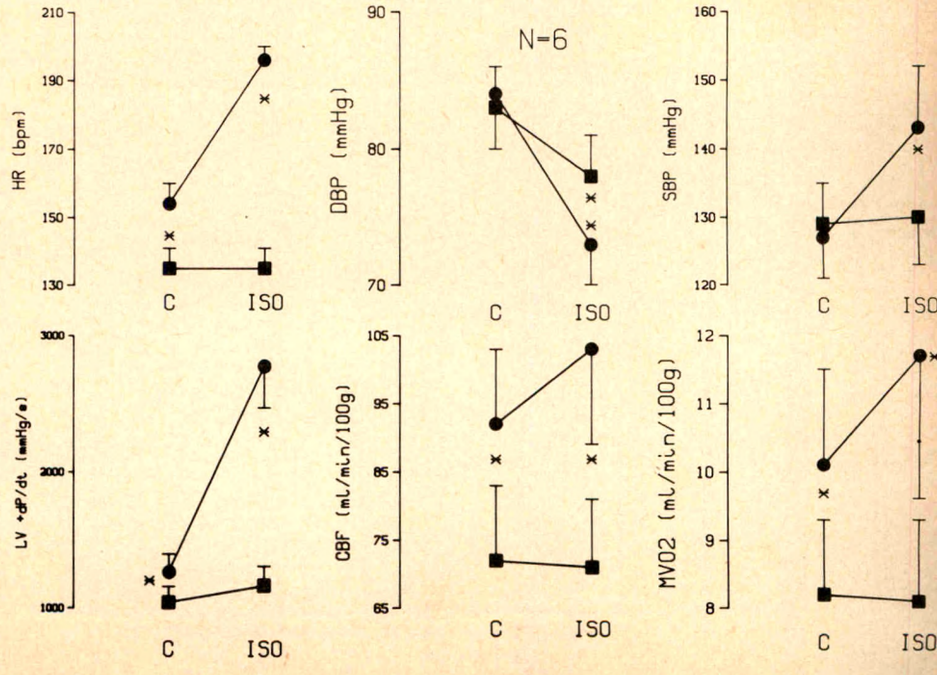

FIGURE 13. Effects of esmolol (310 μg/kg/min) on hemodynamics, coronary blood flow (CBF) and myocardial oxygen consumption (MVO_2). Asterisk above C indicates that esmolol significantly ($p < 0.05$) reduced the variable. The effect of isoproterenol (ISO) infusion (0.25 μg/kg/min for 10 minutes) on these variables was also measured in the absence and presence of esmolol. Asterisk above ISO indicates a significant change in the variable by isoproterenol at the $p < 0.05$ level vs control. DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ● = saline; ■ = esmolol.

TABLE IV Effect of Plasma on Red Blood Cell (RBC) Esmolol Esterase Activity in Dog Blood

Fraction	% Whole Blood Activity*
Washed RBCs	
+ boiled plasma	52.4 ± 2.4 (2)
+ 25% plasma†	65.4
+ 50% plasma	72.3
+ 100% plasma	92.3 ± 10.4 (4)
+ <10K plasma fraction‡	55.0 ± 4.5 (2)
+ <100K plasma fraction	55.0 ± 4.7 (2)
+ <300K plasma fraction	75.0 ± 7.4 (2)
+ >300K plasma fraction	101.3 ± 2.4 (2)

* The in vitro half-life in dog blood was 12.7 ± 4.8 minutes (4). Values are expressed as mean ± standard deviation.
† The percentages refer to the amount of plasma in 1 ml of blood.
‡ Plasma fractions were collected using an Amicon Ultra-Filtration system.
The numbers in parentheses equal the number of experiments.

mediate esterase inhibition because of the rapid metabolism of esmolol in blood and subsequent separation of esmolol from its primary acid metabolite using accepted analytic techniques.

Two independent studies in dogs have shown excellent correlation between the time course and degree of β blockade and the esmolol concentration in blood. In 1 study,[26] esmolol was infused at 3 dosages, each maintained for 1 hour. The degree of β blockade was tested at 10-minute intervals. Steady-state levels of β blockade were rapidly induced by esmolol infusion and the degree of blockade was dose-dependent. Also, β blockade rapidly decayed after esmolol infusion ended. These effects closely followed the blood levels of esmolol. Thus, steady-state levels of esmolol were quickly established and closely followed the infusion rates. Also, the esmolol blood levels rapidly declined after the end of infusion in parallel with the degree of β blockade. An excellent linear relation between the log of the steady-state blood level of esmolol and the degree of β blockade was observed. The average concentration of esmolol, which produced 50% inhibition of isoproterenol-induced tachycardia, was 185 ± 40 ng/ml in this study.

An additional study examined more closely the onset characteristics of β blockade with esmolol.[27] In this study a 500 μg/kg/min loading dose of esmolol was administered for 1 minute followed by a maintenance infusion at varying doses. To examine the onset of β blockade on a moment-to-moment basis, a constant intravenous infusion of isoproterenol was used to provide a continuous stimulation of β receptors. Figure 14 shows the time course of both β blockade and the esmolol blood level during and after 3 infusions of esmolol. The onset of β blockade was extremely rapid, following within seconds of initiation of esmolol administration. Peak blockade occurred within 5 minutes at each dose. Good correlation between the level of esmolol and the degree of blockade was achieved except at the earliest time, at which the degree of blockade lagged behind the blood levels of the drug, which were changing rapidly during this period. There was excellent correlation between the decay of blood levels postinfusion and the decay of β blockade in these experiments. In both this study and the previously described studies, the postinfusion esmolol concentration decayed with a disappearance half-life of approximately 10 minutes.

The pharmacokinetic profile of esmolol was determined in conscious dogs after a single intravenous bolus of 10 mg/kg and after a continuous intravenous infusion of 200 μg/kg/min for 2 hours.[28] The key pharmacokinetic parameters of esmolol were similar after bolus and intravenous infusions. A rapid decrease in the esmolol blood concentration occurred, in part as a result of distribution from blood to tissue but, more importantly, due to rapid metabolism of the com-

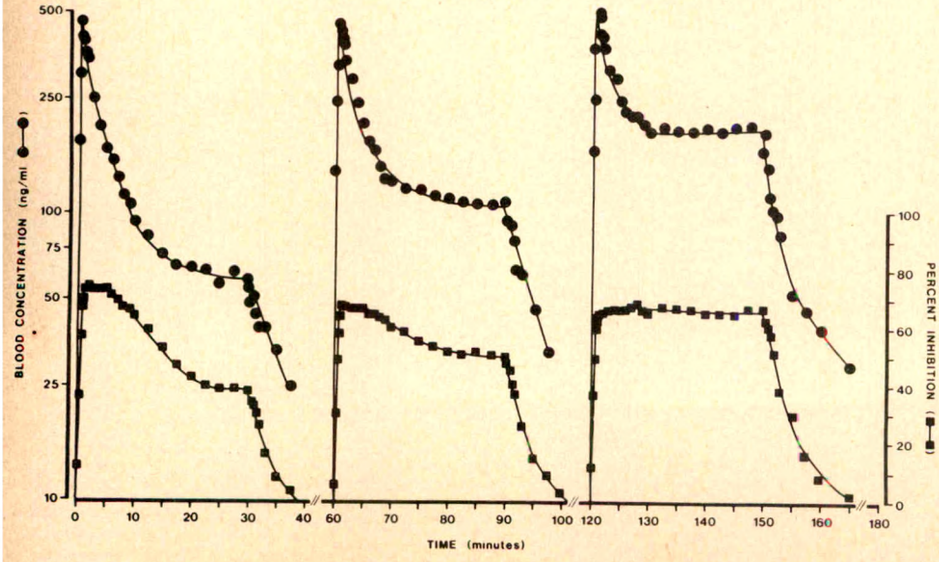

FIGURE 14. Relation between the time course and magnitude of β blockade and the change in blood concentrations of esmolol during and after infusion of esmolol. Percent inhibition refers to the inhibition of isoproterenol-induced tachycardia. Esmolol doses were 12.5, 25 and 50 μg/kg/min, each preceded by a loading dose of 500 μg/kg/min.

pound by blood esterases during transport through the vascular bed. The latter conclusion is supported by the finding that the total body clearance of esmolol (350 ml/kg/min) is greater than resting cardiac output in dogs.

Metabolism of esmolol: The major pathway of esmolol metabolism is hydrolysis of the methyl ester, resulting in methanol and the primary acid metabolite, ASL-8123.[29] Although the metabolite can be shown to produce β blockade, it possesses extremely low affinity for β receptors, with a pA_2 of 3.8. Thus, ASL-8123 is 1,500-fold less potent than esmolol.

Metabolism of esmolol takes place rapidly and extensively in whole blood, and in both dog and human blood the esterase is located in red blood cell cytosol. Unlike most therapeutic agents containing esters, esmolol is totally unaffected by plasma cholinesterase. Under standard in vitro conditions the half-life of esmolol in dog and human whole blood was 12.5 and 27.1 minutes, respectively. For full enzymatic activity the esmolol esterase in red blood cell cytosol requires a heat labile, high-molecular-weight plasma component (Table IV). Washed red cells from dogs contain only half of the original activity of whole blood. Activity is restored by re-addition of plasma or a high-molecular-weight plasma fraction. The enzyme is not inhibited to any significant degree by cholinesterase inhibitors such as physostigmine or echothiophate, but is totally inhibited by sodium fluoride.

No metabolic interactions have been observed between esmolol and other ester-containing molecules of clinical relevance. These findings are consistent with esmolol being metabolized by a blood esterase different from these agents. Also, in anesthetized dogs, esmolol infusion of 100, 300 and 500 μg/kg/min did not modify the magnitude or duration of neuromuscular blockade in response to succinylcholine.

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Discussion

Dr. Reves (Durham, North Carolina): I was intrigued with your intact dog data that showed dose-dependent effects in left ventricular dP/dt, right heart contractile force and heart rate. It seemed to me that in decreases in contractility, the slope was steeper than with heart rate, which is what we have seen, too. How does this compare with other drugs, and do you think this is more of a negative inotrope drug than a negative chronotrope?

Dr. Gorczynski (McGaw Park, Illinois): I do not know for sure; the contractility decreases are confounded by the fact that heart rate also decreases. A proper comparison would be to compare the slopes when you pace the animals—comparing the slope of dP/dt under pacing conditions with the slope of heart rate. I think two things are going on: a decrease in heart rate, which by itself is probably going to decrease contractility (i.e., negative staircase), and then there is the added effect of esmolol on top of that.

Dr. Reves: But how does esmolol compare with something like propranolol?

Dr. Gorczynski: They are very similar, in our hands at least.

Dr. Reves: The slopes look the same?

Dr. Gorczynski: Yes.

Dr. Sonnenblick (Bronx, New York): I think one thing ought to be clarified. In terms of reducing contractility, how directly toxic is the drug to the myocardium? In your findings, there was very little evidence of it. On the other hand, the clinical state of the animal and his level of catecholamines is going to be secondary, which is withdrawal of catecholamines—which is not a direct depression of the heart. Just by withdrawing catecholamines, the heart rate usually will be more affected than the contractility. In most β-blocker preparations, you can lower heart rate with small amounts of β blockade, and then it takes more drug to produce decreases in contractility. I am not sure why one necessarily has to have a parallel between the two.

Dr. Morganroth (Philadelphia, Pennsylvania): Dr. Sonnenblick, how would you go about comparing esmolol with a drug such as propranolol in terms of direct negative inotropic effect? In our supraventricular tachycardia data, esmolol had a more profound effect on blood pressure than propranolol, which, of course, has some theoretical benefits in a postoperative cardiac surgery patient. But the question is whether there is a way to isolate, in a model, the negative inotropic effects in a comparative manner.

Dr. Sonnenblick: In the absence of catecholamines, looking at the tissue directly reveals no difference. But once you have rapid tachycardia with a high catecholamine state, the clinical response is not just in the myocardium, and the blood pressure is usually not a function of contractility, unless the cardiac output is very limited. I think you may be looking at separate effects. I would not equate blood pressure with contractility.

Dr. Morganroth: Therefore, the differential effects will show later, and apparently with esmolol the differences may just be due to an unbalanced group in terms of homogeneity of these factors.

Dr. Gorczynski: Keep in mind also that when you compare esmolol with propranolol, it is like comparing apples and oranges. Reflex vasoconstriction is always greater in the presence of propranolol than it is in the presence of a very cardioselective β blocker.

Dr. Sonnenblick: I think another thing that will come out in the clinical pharmacology section is that all the β blockers will drop cardiac output acutely. The vascular responses to that in the periphery can be somewhat complex, but that does not directly mean that the myocardium is depressed; I think this points out that it may be a separate issue.

Dr. Gray (Los Angeles, California): You have shown that the half-life is very short and the clearance rate is very rapid. Most of your experiments appear to be over a relatively short period of infusion. I think there was one where you went up to 200 minutes. Have you any experience with longer infusions, or any reason to believe that if you have longer infusions, there would be a different metabolic clearance rate or different duration of action?

Dr. Gorczynski: Yes, we have given it for up to 5 hours to determine pharmacologic effects and found a very short half-life. We have also, in our toxicity studies, gone up to 14 days of continuous administration and found blood levels fall just as rapidly.

Dr. Gray: This is in the intact dog?

Dr. Gorczynski: Yes. Conscious dogs.

Dr. Morganroth: You should not necessarily limit esmolol to patients with ischemic heart disease because the use of β blockers in patients with cardiomyopathy is an interesting problem. This may be an ideal agent to screen patients for those who may do well with β blockade in general idiopathic cardiomyopathy.

Dr. Sonnenblick: Absolutely.

Dr. Kirshenbaum (Boston, Massachusetts): We tried to answer that question. Every patient in the ischemic study—with acute infarct or unstable angina—who tolerated esmolol was able to go on to an oral β blocker and tolerate that with roughly equivalent heart rate reductions. It is hard to say exactly equivalent, because the clinical situation in the acute ischemic episode versus several days later obviously changes. The other way around is the fact that some patients failed to tolerate esmolol when they were acutely ill. We did not predict that they would not tolerate an oral long-acting β blocker several days down the line, but, again, their

clinical hemodynamic state was very different 3 or 4 days later. We found it very convenient that if a patient tolerates esmolol, we were very comfortable about starting a long-acting cardioselective β blocker, without concern over precipitating significant failure or hypotension.

Dr. Iskandrian (Philadelphia, Pennsylvania): I think it is very important for clinical research to determine that answer. There are many patients in that group and they are facing cost containment pressures plus the hesitation about surgery in such patients. Many are resorting to β blockers for them, and it would be convenient to be able to tell the physician in a couple of hours: Yes, your patient would tolerate x amount of drug if he can tolerate the infusion of a very short-acting β blocker.

Dr. Gorczynski: The only problem with this approach is that showing that someone can tolerate β blockade with esmolol at one point in time really does not have strong predictive value in estimating what that patient can tolerate at another point in time if autonomic conditions are changing, such as in acute myocardial infarction.

Clinical Pharmacology, Pharmacodynamics and Interactions with Esmolol

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The clinical pharmacology and pharmacodynamic data from several clinical trials are summarized. The pharmacokinetic profile of esmolol alone and in the presence of digoxin, morphine and warfarin was studied. Conversely the effect of esmolol on these drugs was monitored. No clinically important effects were observed on vital signs, blood chemistry or hematology. The pharmacokinetic interactions associated with administration of these drug combinations were statistically significant in several cases, but they were not considered to be of clinical importance. (Am J Cardiol 1985;56:14F–18F)

Esmolol HCl is an ultrashort-acting, cardioselective β-adrenergic blocking agent proposed for use in the therapy of supraventricular tachyarrhythmias, perioperative tachycardia and hypertension, postoperative hypertension and acute myocardial ischemia.[1] Esmolol's short half-life (approximately 9 minutes) provides an element of safety in treating critically ill patients that is not present in currently available β-blocking agents. In animals esmolol has been shown to have 1/40 of the β-blocking potency of propranolol.[2] Esmolol demonstrated no intrinsic sympathomimetic activity in animals and no significant membrane stabilizing activity at therapeutic dosages. Esmolol inhibits the β_1 receptors located chiefly in cardiac muscle, but at 40- to 100-fold higher doses it also inhibits β_2 receptors located chiefly in the bronchial and vascular musculature, respectively. This report summarizes the clinical pharmacology data of esmolol from several studies.

Metabolism and Pharmacokinetics

Esmolol is metabolized by esterases that are located in red blood cells and not by plasma cholinesterases.[3] The hydrolysis of the esmolol ester results in the formation of an acid metabolite (ASL-8123 or 3-[4-(2-hydroxy-3-(isopropylamino)propoxy)-phenyl]propionic acid) and methanol. In vitro and in vivo animal studies have shown that the acid metabolite is only 1/320 as potent as esmolol as a β-adrenergic blocking agent. Methanol blood levels, monitored in subjects receiving esmolol for 6 hours at 300 μg/kg/min and 24 hours at 150 μg/kg/min, were usually within endogenous levels and always at least 2 orders of magnitude below levels associated with methanol toxicity.[1]

The fact that esmolol metabolism is based in the vascular system makes it inherent that its metabolism is both rapid and complete. Less than 2% of the drug is excreted unchanged in the urine. Within 24 hours of discontinuation of infusion, 73 to 88% of the dosage has been accounted for in the urine as the acid metabolite of esmolol. Also consistent with the rapid metabolism of esmolol is the finding that it is only moderately protein bound (55% to human plasma protein). The acid metabolite has an even weaker affinity for protein (10% binding to human plasma protein).

Esmolol has been used clinically in the range of 25 to 300 μg/kg/min. Blood levels obtained and pharmacokinetic parameters calculated therefrom have been found to be linear in this dosage range. Esmolol has a rapid distribution half-life of about 2 minutes and a short elimination half-life of about 9 minutes.[4] The total body clearance of esmolol reflects these short half-lives. Total body clearance in man was found to be approximately 20 liters/kg/hr. Since this is about 3 times greater than cardiac output, the metabolism of esmolol is obviously not limited by the rate of blood flow to metabolizing tissues such as the liver. This is consistent with the data showing that erythrocyte esterases are responsible for the hydrolysis of esmolol.

The kinetics of the acid metabolite have also been shown to be linear over the dose ranges studied. The elimination half-life of this metabolite is about 3.7 hours while the total body clearance is approximately equivalent to the glomerular filtration rate.[4]

Because of esmolol's rapid clearance and short half-life, it can be easily titrated to either increased or de-

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creased blood levels within minutes. Using a loading dose, steady-state blood levels of esmolol for dosages of 50 to 300 μg/kg/min were obtained within 5 minutes.[4,5] As previously stated these levels are linearly related to the dose administered over this dosage range. Equally striking is the fact that blood levels of esmolol are not detected approximately 30 minutes after discontinuation of the infusion. Ten to 20 minutes after discontinuation of esmolol infusion substantial recovery from the β blockade is routinely seen in patients.

Pharmacodynamic Studies with Esmolol

Clinical pharmacology studies in normal volunteers confirm the β-blocking activity of esmolol; they show reduction in heart rate at rest and during exercise and inhibition of isoproterenol-induced increases in systolic blood pressure, decreases in diastolic blood pressure and increases in heart rate.[6,7]

The relative cardioselectivity of esmolol was demonstrated in patients with asthma and in patients with chronic obstructive pulmonary disease (COPD).[8] In asthmatic patients, esmolol, 300 μg/kg/min, produced a slight decrease in specific airway resistance and slightly increased the sensitivity to induced bronchoconstriction. These effects were not clinically significant, and esmolol was well tolerated by these patients. No patients were discontinued from the study. Six of the patients also received intravenous propranolol and, at 1 mg, 2 of them experienced significant symptomatic bronchospasm requiring bronchodilator treatment. In addition, propranolol induced bronchospasm in 1 patient at the 5-mg dose. In approximately 60 patients with COPD, no adverse pulmonary effects were observed during clinical studies of esmolol for treatment of supraventricular tachycardia or in perioperative settings.

In a small study in patients with acute ischemic heart disease (unstable angina pectoris or acute myocardial infarction), esmolol, 300 μg/kg/min, decreased cardiac index and systemic vascular resistance but did not affect left ventricular filling pressure. Cardiac index returned to baseline levels during continued maintenance infusions of esmolol; systemic vascular resistance returned to baseline levels within 30 minutes after infusion.

In a trial using patients with chronic atrial fibrillation,[9] esmolol produced a significant dose-dependent decrease in ventricular rate. A dose correlation was observed between blood concentration of esmolol and reductions in heart rate. Furthermore, blood levels of the acid metabolite were found for some time after discontinuation of esmolol infusion and disappearance of esmolol blood levels, but were not associated with β blockade.

Finally, esmolol, when infused in the dose range of 100, 200 or 300 μg/kg/min, effectively attenuated tachycardia and increases in the rate-pressure product induced by endotracheal intubation compared with placebo. The response was dose-related.[10]

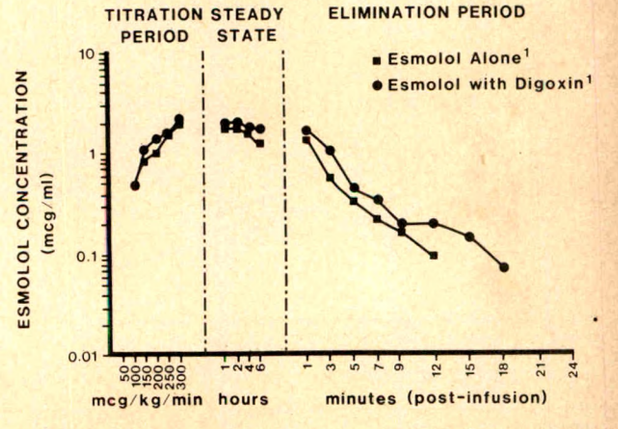
Study Design

To study possible drug interactions, clinical trials were conducted in which digoxin,[7] morphine[11] and warfarin[11] were coadministered with esmolol. All drugs were studied in healthy normal male volunteers. Each study consisted of 3 study periods: esmolol alone, second drug alone and esmolol in combination with the second drug. The pharmacokinetics of each drug were monitored as a sensitive indicator of any changes occurring during concomitant therapy. Thus, the pharmacokinetics of digoxin, morphine and warfarin were evaluated alone and in the presence of esmolol; furthermore, esmolol was evaluated alone and in the presence of digoxin, morphine or warfarin. Comparisons were then made between periods of treatment to detect differences resulting from concomitant therapy. Digoxin, warfarin and esmolol were studied under steady-state conditions. Morphine was studied after a single intravenous bolus.

Studies were carried out at the clinical research unit of Hahnemann University. These were all open-label studies approved by institutional review committees and written informed consent was obtained from all volunteers. All subjects were screened to ensure that they were healthy and that their prestudy laboratory parameters were within normal ranges.

Results and Discussion

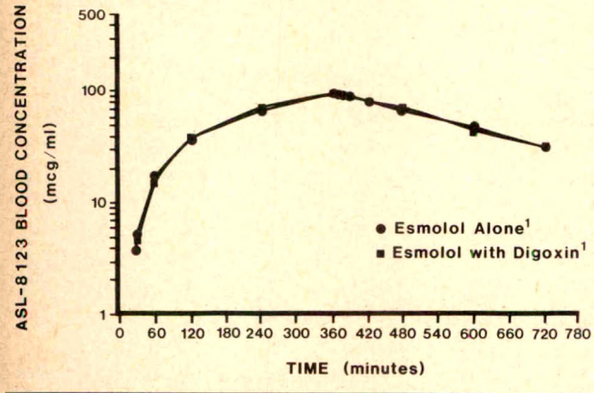
Esmolol-digoxin interaction: Interactions with digoxin were studied in 12 normal male subjects.[7] The pharmacokinetics of esmolol alone, during and after a 6-hour infusion (300 μg/kg/min) and the pharmacokinetics of digoxin alone (administered to obtain blood levels of 0.8 to 2 ng/ml) at steady state were compared with the same conditions but administered concurrently. The steady-state blood levels, total body clearance, half-lives and volume of distribution for esmolol did not show any significant changes between esmolol and esmolol-digoxin treatments. The mean concentrations for esmolol during the 2 treatments are shown in Figure 1. Additionally, no significant changes in half-lives or maximal blood levels of the acid metabolite of esmolol were seen between esmolol and esmolol-digoxin treatments. The mean concentrations for the



1. Mean of 11 subjects.

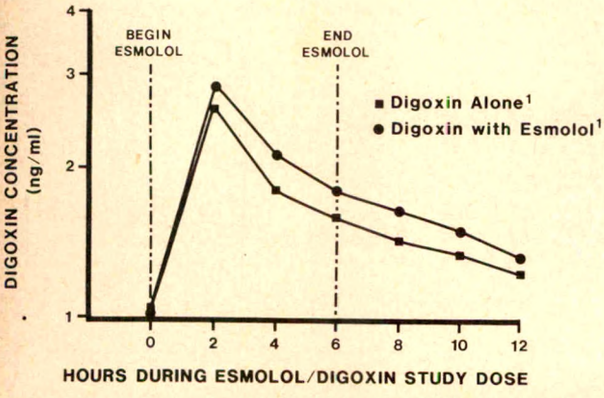
FIGURE 1. Mean esmolol blood levels in 11 normal subjects are shown when esmolol was given alone (■) and in the presence of steady-state levels of digoxin (●). Esmolol infusion was initiated with a titration period and maintained at 300 μg/kg/min for 6 hours.

acid metabolite of esmolol during the 2 treatments are shown in Figure 2. A slight influence of esmolol was seen on digoxin concentrations at 4 hours after dosing, as shown in Figure 3. Serum digoxin levels were increased by 9.6 to 19.2% during esmolol-digoxin treatment compared with digoxin alone. However, only the 4-hour digoxin serum levels were significantly elevated when the 2 treatments were compared by subject. Two- and 6-hour samples did not show any significant differences. The total area under the digoxin-concentrations-versus-time curve during the 6-hour esmolol infusion was significantly higher in the presence of esmolol than when digoxin was given alone. No significant change in peak digoxin levels was observed. The changes in digoxin pharmacokinetics are not considered to be of a clinically significant magnitude. However, caution should be exercised in using the drugs in combination because digoxin levels may be slightly elevated during esmolol infusion.



1. Mean of 11 subjects.

FIGURE 2. Mean blood levels of the acid metabolite of esmolol (ASL-8123) in 11 normal subjects are shown when esmolol was given alone (●) and in the presence of steady-state levels of digoxin (■). Esmolol infusion was initiated with a titration period and maintained at 300 μg/kg/min for 6 hours.

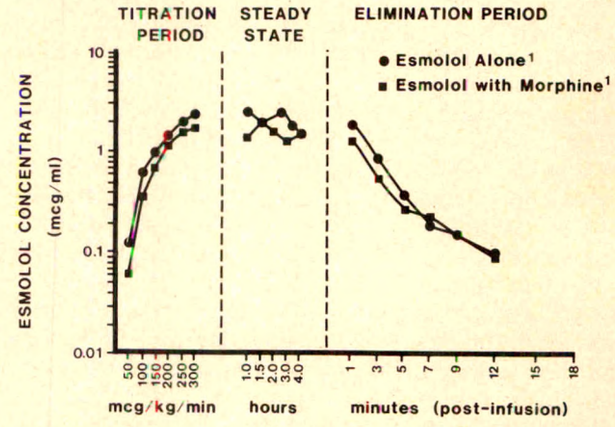


1. Mean of 11 subjects.

FIGURE 3. Mean digoxin levels in 11 normal subjects are shown when digoxin was given alone (■) and in the presence of esmolol (●); esmolol infusion lasted 6 hours. Digoxin had been given to a steady-state therapeutic level before the study period shown in this figure.

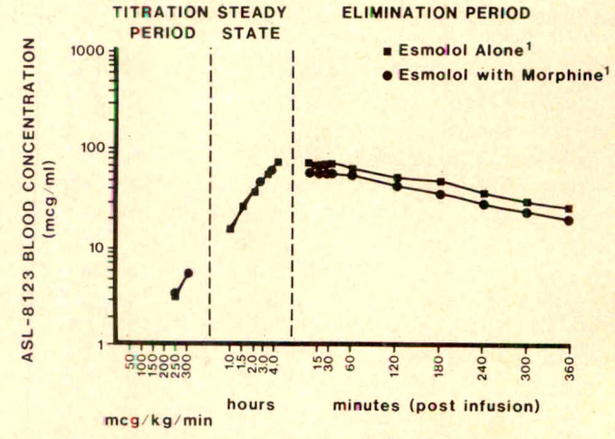
Esmolol-morphine interaction: The interactions between morphine and esmolol were studied in a similar trial. Ten normal men were infused with esmolol alone for 4 hours (300 μg/kg/min). The next day each received a slow injection of morphine sulfate (3 mg) and on the third day similar doses of morphine and esmolol were coadministered. The pharmacokinetics of esmolol and morphine alone were compared with the pharmacokinetics of the 2 drugs when they were coadministered.

Steady-state blood levels of esmolol during coadministration of morphine were generally higher (9 of 10 subjects) than during esmolol treatment alone. However, because of the variability in the individual blood level determinations only 2 of the 10 subjects showed statistically significant increases in steady-state esmolol levels. As shown in Figure 4, the mean steady-state



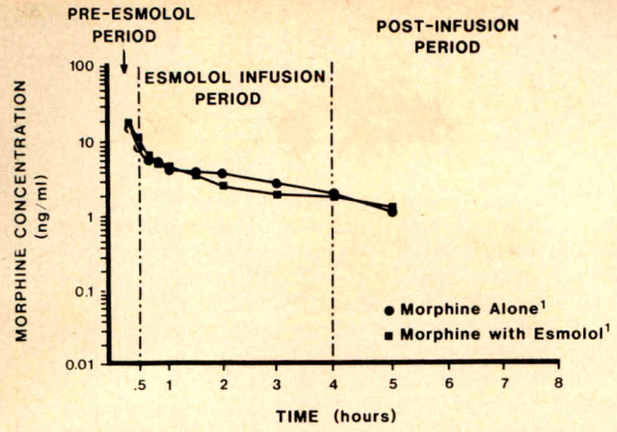
1. Mean of 10 subjects.

FIGURE 4. Mean esmolol blood levels in 10 normal subjects are shown when esmolol was given alone (●) and in the presence of steady-state levels of morphine (■). Esmolol infusion was initiated with a titration period and maintained at 300 μg/kg/min for 4 hours.



1. Mean of 10 subjects.

FIGURE 5. Mean blood levels of the acid metabolite of esmolol (ASL-8123) in 10 normal subjects are shown when esmolol was given alone (■) and in the presence of steady-state levels of morphine (●). Esmolol infusion was initiated with a titration period and maintained at 300 μg/kg/min for 4 hours.



1. Mean of 10 subjects.

FIGURE 6. Mean morphine levels in 10 normal subjects are shown when morphine was given alone (●) and in the presence of esmolol (■); esmolol infusion lasted 4 hours. Morphine had been given to a steady-state therapeutic level before the study period shown in this figure. Morphine was studied after single intravenous infusion of morphine sulfate.

blood level of esmolol was significantly higher (46%, $p < 0.05$) during the morphine-esmolol period. Morphine, however, had no effect on the half-life of esmolol. It also had no effect on the blood levels, total body clearance, elimination rate constant and terminal elimination half-life of the acid metabolite of esmolol. A plot of mean concentrations for the acid metabolite in all subjects is summarized in Figure 5.

Morphine serum levels were similar during both morphine and morphine-esmolol treatment periods. Thus, neither esmolol nor its acid metabolite had any effect on the area under the concentration-time curve or the elimination half-life of morphine. The mean morphine levels are shown in Figure 6.

Based on the results of this study, esmolol caused no changes in the pharmacokinetics of morphine. Morphine had no effect on the pharmacokinetics of the acid metabolite of esmolol. Morphine, however, may increase steady-state blood levels of esmolol. Although caution should be exercised when administering esmolol and morphine simultaneously, the short half-life of esmolol will allow rapid titration of steady-state levels of esmolol by changes in the infusion rate.

Esmolol-warfarin interaction: Preliminary data of a similar interaction study between esmolol and warfarin in normal men showed that the concomitant administration of esmolol and warfarin does not influence warfarin plasma levels. There are no differences in area under the curve, Cmax (maximum plasma concentration) and Tmax (time to reach Cmax) when comparing warfarin with warfarin plus esmolol. Esmolol concentrations are equivocally higher when given with warfarin.

The studies with digoxin, morphine and warfarin show that they are well tolerated when administered alone and in the presence of steady-state levels of esmolol.

In summary, esmolol is well tolerated when given in the presence of digoxin, morphine or warfarin. Conversely these drugs were also shown to be well tolerated when given in the presence of steady-state levels of esmolol (300 μg/kg/min dose). No clinically important effects were observed on vital signs, blood chemistry or hematology. The pharmacokinetic interactions associated with administration of these drug combinations were statistically significant in several cases but they are not considered to be of clinical importance. In view of the results of these interaction studies, esmolol should be administered cautiously to patients being treated concurrently with digoxin, morphine or warfarin. However, the short half-life enhances the safety of esmolol use because it allows rapid alteration of blood esmolol levels by changing its infusion rate.

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Discussion

Dr. Sonnenblick (Bronx, New York): The one thing about esmolol that does seem a bit different from the usual β blockers is the extent of the fall in blood pressure, which one would not predict in the usual β response in which there is a fall in cardiac output, an increase in resistance and very little change in blood pressure. What were the ranges of the change in blood pressure and, although on the average they were tolerated, were they tolerated individually?

Dr. Lowenthal (Philadelphia, Pennsylvania): They were tolerated in the total group. Interestingly, in normal volunteers during the drug interaction studies, there was hardly any significant change at all in blood pressure, and even less change in heart rate. There were times when we thought we were giving saline or placebo because we clearly did not see any pharmacodynamic effect.

Dr. Iskandrian (Philadelphia, Pennsylvania): Dr. Lowenthal, why were these 3 drugs chosen to study for interactions? I ask that because in that clinical setting I can think of more commonly used drugs, such as nitrates, dopamine, dobutamine and heparin, rather than warfarin, morphine or digoxin.

Dr. Lowenthal: That is a very valid point. Patients who are admitted to a coronary care unit with myocardial infarction and chest pain are frequently given morphine. This was a study to try and mime a true clinical setting in which esmolol might be given to such a patient, who is also on morphine. If esmolol caused a higher availability of morphine in a myocardial infarction setting, the results of future research with myocardial infarction patients may be clouded because of esmolol's effect on blood levels of morphine. This interaction study was done to prepare for esmolol studies in patients with myocardial infarction. Digoxin was studied because many patients who will receive esmolol will also be given digoxin, and the therapeutic window of digoxin is known to be very narrow. We tested warfarin because there are a number of patients who are on anticoagulant therapy. Because warfarin is a highly protein-bound drug, it was tested as a representative of the highly protein-bound class of drugs. Many drug interactions are a direct result of altered protein binding.

Dr. Sonnenblick: Just for the record, I would like Dr. Lowenthal to clarify one thing. In a person without a compromised circulation and with a normal heart rate, what are the limits to how far the drug has been given, and are there any other cardiovascular effects to be seen? You were saying that there was no change in blood pressure and that heart rate at rest does not change. Is that really the result?

Dr. Lowenthal: Yes, when we gave esmolol up to 300 μg/kg/min to normal volunteers, no changes were seen in heart rate and only small changes in blood pressure. The other thing that has not been done, and I have discussed this issue with other investigators, is to really see whether there is β blockade in these normal volunteers. This could be done simply by giving an isoproterenol challenge or administering some exercise studies.

Dr. Gray (Los Angeles, California): First a comment, then some questions. I think the diversity of responses that you are alluding to, and which I believe that we can attest to in our clinical setting, may, in fact, relate to something that Dr. Sonnenblick mentioned. That is, the response to this drug and other β blockers must be very dependent on catecholamines or the sympathetic state of the patient. I am sure that the situations in which the drug is tested, whether it is a resting, relaxed volunteer or a critically ill patient in an acute care setting, are very different situations and will demand different responses to the drug. I think the situation is nowhere near as clear as when the patient in the operating room is given various levels of anesthesia and we are looking at some physiologic response. This response may well be a response to the severity of anesthesia or to the depth of anesthesia. But I have two questions. The first question relates to the drug interaction with warfarin: did you see a perturbation of the prothrombin time when you gave esmolol?

Dr. Lowenthal: No.

Dr. Gray: So you would not expect an enhancement of the coumadin effect if esmolol were instituted in a previously stabilized, anticoagulated patient?

Dr. Lowenthal: That is correct.

Dr. Gray: The other question relates to the issue of the metabolic activity of ASL-8123. If I am correct, I believe you hinted at some possible physiologic effects of this moiety—I am not sure if that is correct. In any case, it did look like there was quite a prolonged period of elimination. The reason I am asking about this is that when we gave esmolol to patients with tachycardia, for instance, over a period of many, many hours, the heart rate returned to baseline very slowly when we stopped the drug. This implies that there may be either some change in the physiologic basal state of the patient or there may be some prolonged effect that is not seen with the brief infusion and cessation.

Dr. Lowenthal: I appreciate your comments, Dr. Gray, especially in regard to basal sympathetic tone in "normal" people versus patients with cardiovascular disease in the intensive care setting. However, although we did not measure catecholamines, I can tell you that when volunteers are put in bed and have various intravenous lines in their arms, and do not know the effects of this "investigational or experimental drug" and are clearly in a subservient position, that, too, can induce some increase in adrenergic tone. Clearly it is relative. However, we still did not see any changes in heart rate or blood pressure.

Dr. Gorczynski (McGaw Park, Illinois): I would like to respond to the pharmacodynamic activity of the metabolite. We tested this in two situations and if one gives extremely high metabolite concentrations, one can demonstrate a reduction in isoproterenol-driven tachycardia. The metabolite requires 350-fold higher concentrations than you need with esmolol to blunt tachycardia, both in intact animals as well as in vitro. These are very high millimolar concentrations.

Electrophysiology of Esmolol

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The electrophysiologic characteristics of esmolol were studied in 14 patients. Ten men and 4 women, mean age 57 years, were electrophysiologically evaluated at baseline, and also at 4 to 8 minutes after the administration of a maintenance infusion of esmolol. Plasma samples for esmolol blood levels were drawn at 10 minutes of the maintenance infusion, at the end of the maintenance infusion and 30 minutes after the maintenance infusion was discontinued. Results of this study showed that esmolol has typical β-blocker electrophysiologic effects. Its major action was on sinus node function; it prolonged this basic sinus cycle length but had no significant effect on intrinsic automaticity as reflected by the corrected sinus node recovery time and sinoatrial conduction. Direct effects on atrioventricular (AV) nodal function were reflected by effects on AV nodal conduction and refractoriness. There was no direct effect on atrial function and, as expected, no effect on His-Purkinje or ventricular function. The intensity of esmolol's electrophysiologic effects on sinus node function, AV nodal conduction and AH interval is comparable to those of other β blockers.

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Acute interventions to control atrial tachyarrhythmias frequently require the parenteral administration of β blockers to patients with impaired left ventricular function, who are further compromised by the toxic or metabolic derangements of their acute clinical situation.[1–3] Under these circumstances, patients are particularly susceptible to the negative inotropic and bronchospastic adverse effects of β blockers, which can actually worsen the clinical situation.[4] Thus the development of a very short-acting β blocker—whose electrophysiologic and hemodynamic effects could be rapidly initiated and reversed to adapt to the changing requirements of such acute clinical situations—would be of major benefit. Esmolol, a newly developed parenteral β blocker, has an ultrashort elimination half-time (9 minutes) and might satisfy the criterion for a rapidly acting agent to be used in such acute metabolic derangements. We therefore characterized the electrophysiologic effects of esmolol in 14 hospitalized patients undergoing clinical electrophysiologic studies for various indications.

Methods

The characteristics of the study population are outlined in Table I. Ten men and 4 women, mean age 57 years, gave informed consent for the administration of intravenous esmolol after routine clinical electrophysiologic study. Ten of the 14 patients had organic heart disease; most had coronary disease with a previous myocardial infarction. As a group, left ventricular systolic function was mildly decreased, but 3 patients had severe dysfunction (with ejection fractions of 11, 27 and 33%). The most common indication for electrophysiologic study was syncope and the most common finding at clinical electrophysiologic study was an inducible ventricular tachyarrhythmia. The study protocol is illustrated schematically in Figure 1. Patients underwent routine clinical electrophysiologic studies with 3 multipolar electrode catheters positioned under local anesthesia in the high right atrium, atrioventricular (AV) junction and right ventricular apex. Standard measurements of sinus node, AV node, atrial, His-Purkinje and ventricular function were made as outlined in Table II.

After the baseline electrophysiologic study, esmolol was administered in a 2-stage infusion. There was an initial loading phase of 500 μg/kg/min for 3 to 5 minutes, followed by a maintenance infusion of 300 μg/kg/min that was continued until completion of the electrophysiologic measurements, i.e., 8 to 40 minutes. After the maintenance infusion ended, esmolol was allowed to wash out for 30 minutes to achieve baseline conditions. Patients 1 to 5 received a 3-minute loading infusion, while patients 6 to 14 received a 5-minute loading infusion. Electrophysiologic measurements were initiated at 4 to 8 minutes of the maintenance infusion and 30 minutes after termination of the infusion. On average, the measurements were completed in 18 minutes.

Plasma samples for esmolol levels were obtained at 10 minutes of the maintenance infusion, at the end of the maintenance infusion and at 30 minutes after washout. The cuff blood pressures and the sinus cycle length were measured every 5 minutes throughout the course of the experimental protocol.

From the Clinical Electrophysiology Laboratory, Likoff Cardiovascular Institute of Hahnemann University, Philadelphia, Pennsylvania.

Address for reprints: Allan M. Greenspan, MD, Clinical Electrophysiology Laboratory, Likoff Cardiovascular Institute of Hahnemann University, 6617 New College Building, 230 North Broad Street, Philadelphia, Pennsylvania 19102.

TABLE I Patient Characteristics (n = 14)

Age	57 (28–73)
OHD	10 (6—CAD, 3—VHD, 1—CM)
Ejection fraction	48% (11 to 72%)
Indication for EPS	9—syncope, 3—VTA, 1—SSS
EPS findings	6—inducible VTA, 2—CSH, 1—↑HV

CAD = coronary artery disease; CM = cardiomyopathy; CSH = carotid sinus hypersensitivity; EPS = electrophysiologic study; OHD = organic heart disease; SSS = sick sinus syndrome; VHD = valvular heart disease; VTA ventricular tachyarrhythmia.

Statistical evaluations were performed by analysis of variance and all measured values are reported as mean ± standard deviation. Because there were no significant differences by analysis of variance in either the mean plasma esmolol levels or the mean values of electrophysiologic parameters between the 2 groups with differing loading infusions, the data from these groups were pooled and analyzed together.

Results

Electrophysiologic effects during infusion: The major electrophysiologic effects of esmolol were on sinus node and AV nodal function. As shown in Figure 2, esmolol significantly prolonged the basic sinus cycle length and the sinus node recovery time. However, esmolol did not influence the sinoatrial conduction time or the corrected sinus node recovery time. Figure 3 illustrates the direct effects of esmolol on AV nodal

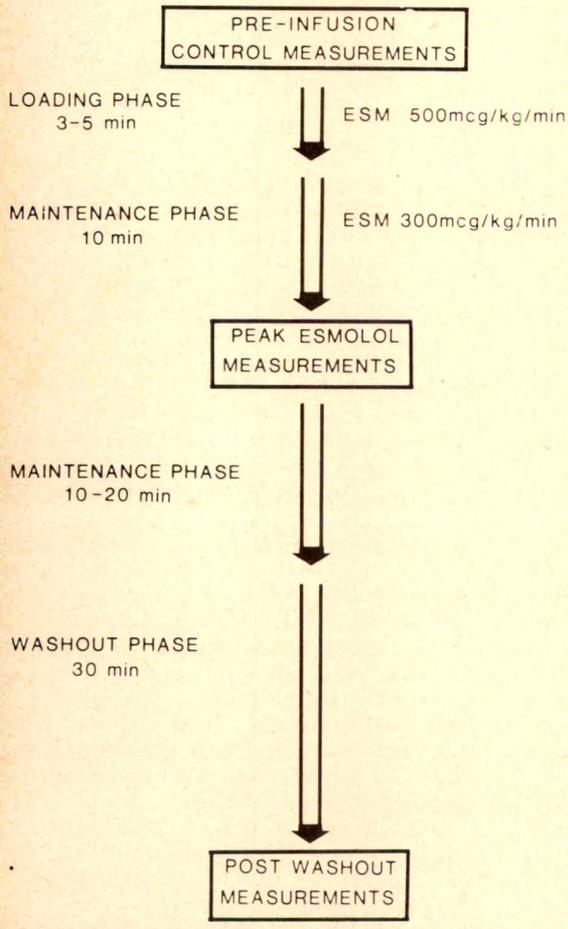

FIGURE 1. Schematic illustration of the experimental protocol. Electrophysiologic measurements were made before the 2-stage esmolol (ESM) infusion, beginning at 4 to 8 minutes of the maintenance phase and 30 minutes after termination of the maintenance phase. Loading dose = 500 μg/kg/min for 3 minutes (5 patients) and 500 μg/kg/min for 5 minutes (9 patients).

TABLE II Measured Electrophysiologic and Electrocardiographic Parameters

- Sinus node function
  - Sinus cycle length
  - Sinus node recovery time
  - Corrected sinus node recovery time
- Atrial function
  - Intraatrial conduction time (PCL 600,450)
  - Atrial effective refractory period (PCL 600,450)
- AV nodal function
  - Shortest PCL 1:1 AV conduction
  - AH intervals (NSR, PCL 600)
  - AV nodal effective refractory periods (PCL 600,450)
  - AV nodal functional refractory periods (PCL 600,450)
  - Retrograde (ventriculoatrial) AV nodal conduction time
- His-Purkinje function
  - Infranodal conduction times (NSR, PCL 600)
- Ventricular function
  - Ventricular effective refractory periods (PCL 600,450)
- Electrocardiographic parameters
  - Heart rate
  - QRS interval
  - PR interval
  - QT interval

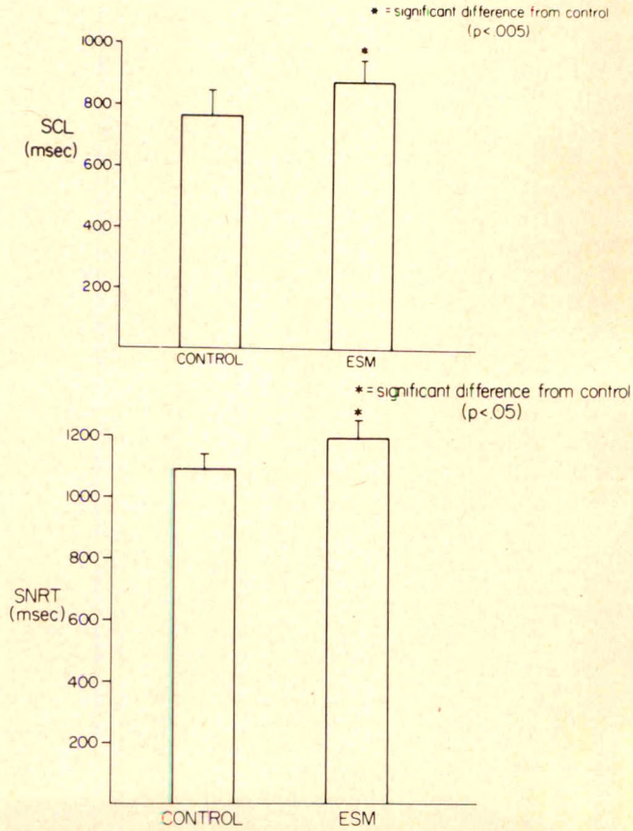

FIGURE 2. Effects of esmolol (ESM) on sinus cycle length (SCL) **top,** and on sinus node recovery time (SNRT) **bottom,** during the maintenance infusion. Esmolol significantly prolonged both SCL and SNRT compared with control values.

TABLE III Esmolol Effects: Blood Pressure and Electrocardiographic Parameters

	Infusion Time		
	Control (n)	Peak Esmolol (n)	Post Esmolol (n)
SBP NSR (mm Hg)	125.6 ± 3.9 (14)	118.6 ± 4.0 (14)	120.1 ± 6.1 (14)
DBP NSR (mm Hg)	73.6 ± 2.9 (14)	74.0 ± 2.2 (14)	72.4 ± 3.5 (14)
SBP 600 (mm Hg)	129.7 ± 6.7 (6)	120.8 ± 3.7 (13)	119.8 ± 6.1 (13)
DBP 600 (mm Hg)	76.3 ± 6.0 (6)	80.1 ± 2.9 (13)	73.7 ± 3.4 (13)
PR interval (ms)	179.6 ± 7.5 (14)	181.6 ± 8.9 (14)	174.6 ± 8.7 (14)
QRS interval (ms)	113.2 ± 11.1 (14)	112.1 ± 9.8 (14)	110.4 ± 9.9 (14)
QT interval (ms)	384.4 ± 11.0 (14)	379.6 ± 11.6 (14)	71.4 ± 12.4 (14)
Heart rate (beats/min)	78.5 ± 3.1 (14)	70.7 ± 3.5* (14)	84.8 ± 3.2* (14)

* significant change from control, $p < 0.05$.
DBP = diastolic blood pressure; NSR = normal sinus rhythm; SBP = systolic blood pressure.

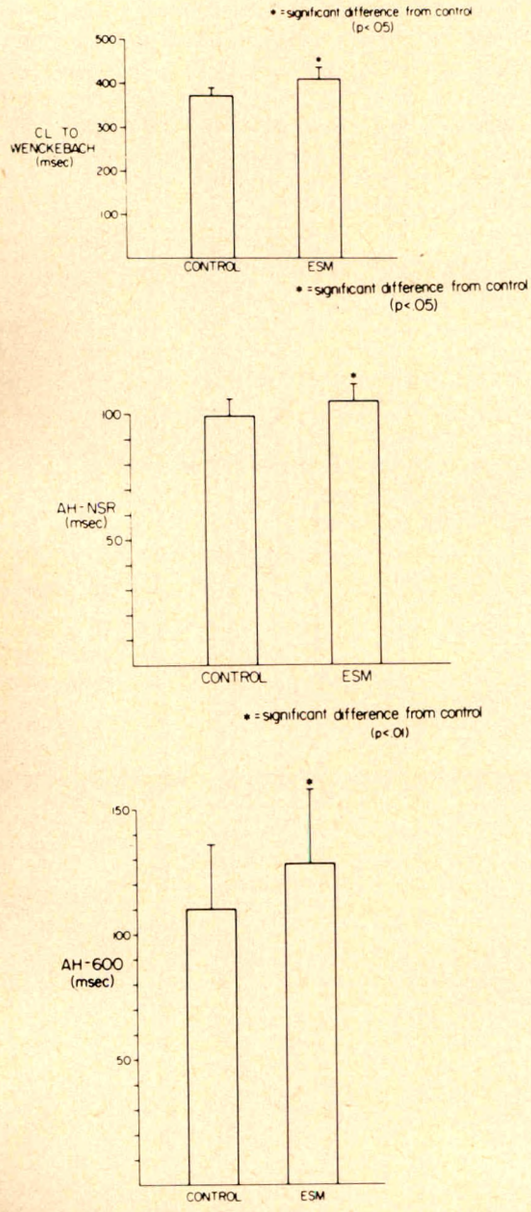

FIGURE 3. Effects of esmolol (ESM) on parameters of AV nodal function during the maintenance infusion. Esmolol significantly prolonged the cycle length to Wenckebach, **top,** the AH interval measured during sinus rhythm, **middle,** and the AH interval at an atrially paced cycle length of 600 milliseconds, **bottom.**

function. Esmolol significantly increased the cycle length at which Wenckebach periodicity developed and the AH interval measured during sinus rhythm and at a paced atrial cycle length of 600 ms. Esmolol, however, did not alter AV nodal refractoriness or retrograde AV nodal conduction time. Esmolol also showed no direct effects on atrial, His-Purkinje or ventricular function.

Electrophysiologic effects after termination of the infusion: All electrophysiologic parameters were remeasured 30 minutes after termination of the infusion when plasma drug levels were projected to be negligible. At this time, most parameters had reverted to predrug control levels, although some parameters fell significantly below control levels, reflecting an overshoot.

Effects on electrocardiographic intervals and blood pressure: Figure 4 illustrates the effects of esmolol during and after the infusion on systolic blood pressure; Table III lists the responses of electrocardiographic intervals to esmolol. There were no significant changes in blood pressure or any of the electrocardiographic intervals during either phase of the protocol.

Time course of the beta-blocking effect: Using the change in sinus cycle length as an index of electro-

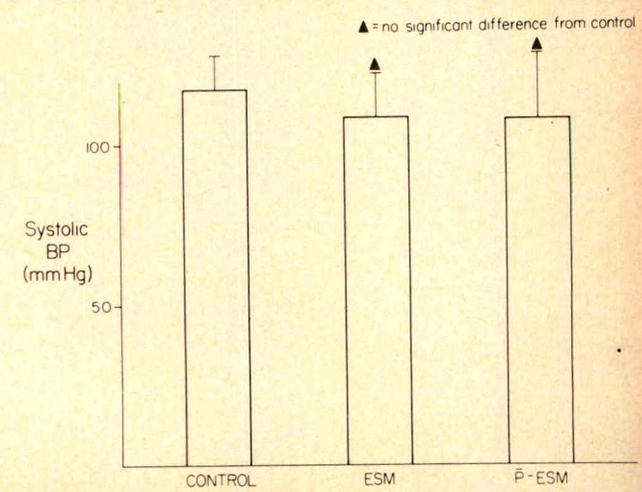

FIGURE 4. Effect of esmolol (ESM) on systolic blood pressure (BP) during, **middle,** and after, **right,** the maintenance infusion. Esmolol did not significantly lower systolic BP during either circumstance.

TABLE IV Esmolol Plasma Levels

Infusion Time	Plasma Level (μg/ml)
Control	<0.05
MP 10 min	0.90 ± 0.54
MP end	1.05 ± 0.42
MP 10 min (300 μg/kg/min × 3 min load)	0.84 ± 0.68
MP 10 min (500 μg/kg/min × 5 min load)	0.97 ± 0.39

MP = maintenance phase.

physiologic β-blocking action, the time course of esmolol's β-blocking effect is shown in Figure 5. Esmolol significantly prolonged the sinus cycle length within 5 minutes of initiating the infusion. The effect was reversed within 5 minutes of terminating the infusion.

Plasma esmolol levels: Table IV lists the plasma esmolol levels present before the infusion and at 10 minutes of the infusion for the total study population and for the 2 subgroups with differing loading doses. There were no detectable esmolol levels before the infusion, and the infusion did produce significant plasma concentrations. There was no significant difference in the plasma levels achieved by the 2 loading doses.

Discussion

General electrophysiologic profile: Esmolol is a newly developed β blocker with rapid pharmacodynamics that might be useful in acute antiarrhythmic interventions to control arrhythmias influenced by alterations in adrenergic tone. A number of studies have examined the electrophysiologic actions of various β blockers administered intravenously and with only minor variation, they have a common electrophysiologic profile. These intravenous β blockers mainly alter sinoatrial nodal and AV nodal function, variably influence atrial function and the corrected QT interval and have no effect on His-Purkinje and ventricular function.[5–11]

The present study demonstrates that esmolol has typical β-blocking electrophysiologic effects. Its major action was on sinus node function; it prolonged the basic sinus cycle length, but had no significant effect on intrinsic automaticity as reflected by corrected sinus node recovery time or sinoatrial conduction. Direct effects on AV nodal function were reflected by effects on AV nodal conduction and refractoriness. There was no direct effect on atrial function and, as expected, no effect on His-Purkinje or ventricular function.

Comparative time course of electrophysiologic effects: Although the onset of esmolol's electrophysiologic effect is no more rapid than other intravenous β blockers, its regression of this action is much faster. Using sinus cycle length as an index, significant electrophysiologic changes were detectable within 5 minutes of initiating the esmolol infusion, as it was for intravenous metoprolol[7] and acebutolol.[8] However, the reversal of esmolol's electrophysiologic effect occurred within 5 minutes of terminating the infusion; in contrast, these effects persisted with the other β blockers for 30 to 45 minutes (Fig. 6).

The rapidity of the reversal of esmolol's electrophysiologic effects compared with other β blockers is paralleled by its comparatively rapid pharmacodynamics. Esmolol's elimination half-time (9 minutes) is

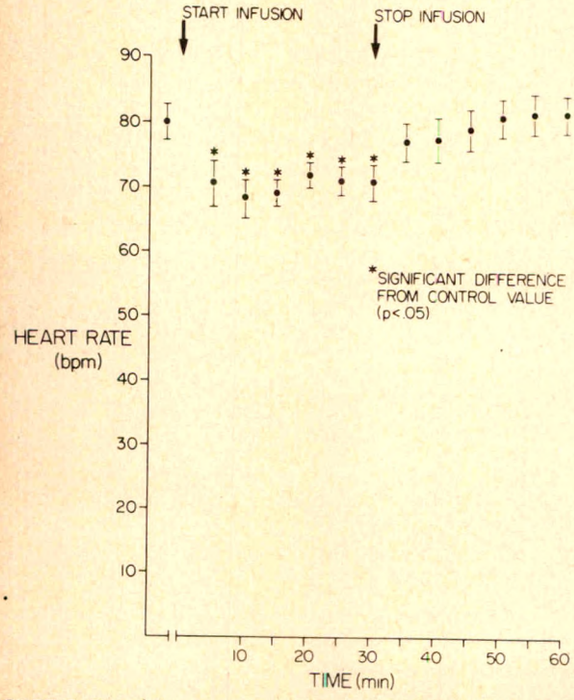

FIGURE 5. Plot of the mean heart rate (ordinate) for the 14 patients versus time (abscissa), before, during and after esmolol infusion. The mean heart rate was significantly reduced compared with control within 5 minutes of initiating the infusion; it increased to control levels within 5 minutes of terminating the infusion. bpm = beats/min.

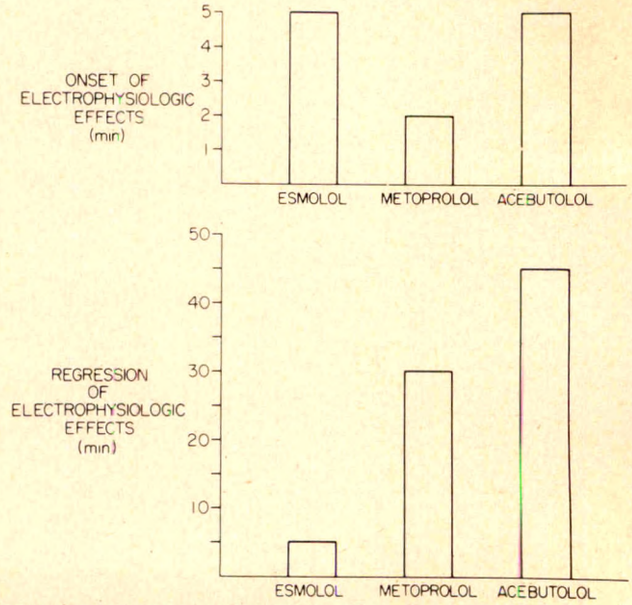

FIGURE 6. Time course of esmolol's electrophysiologic effects that prolong sinus cycle length is compared with those of metoprolol and acebutolol. The onset of esmolol's electrophysiologic effect does not differ from that of the other 2 β blockers; however, its time of regression is quite different.

much shorter than the others, which range from 2 to 3 hours for acebutolol to 6 to 9 hours for atenolol.

Comparative intensity of esmolol's electrophysiologic effects: The intensity of esmolol's electrophysiologic effects on sinus node function is comparable to those of other β blockers. As shown in Figure 7, esmolol prolonged the sinus cycle length to the same degree as metoprolol[7] and acebutolol.[8] Similarly, esmolol's effect on AV nodal conduction characteristics was of similar intensity to those of other β blockers. Esmolol increased the AH interval to an extent similar to metoprolol,[7] timolol[10] and propranolol.[11] In contrast, the electrophysiologic action of esmolol on AV nodal refractoriness was less intense than that of the other β blockers.

Clinical Applications

The efficacy of β-blocking drugs in the control of supraventricular tachyarrhythmias and ventricular ectopy is established.[12,13] In this regard, β blockers are particularly useful in the therapy of supraventricular tachyarrhythmias arising from cardiac structures rich in sympathetic innervation, i.e., sinoatrial and AV nodes, arrhythmias dependent on elevated sympathetic tone or catecholamine levels that occur in acute, toxic metabolic derangements and ventricular arrhythmias associated with inhomogeneous repolarization secondary to inhomogeneous sympathetic neural influences. The specific clinical utility of esmolol would be in the treatment of arrhythmias usually responsive to β blockers but occurring in patients with a high risk for untoward effects of β blockade. In patients with underlying left ventricular dysfunction, obstructive pulmonary disease or myocardial depressant effects of the toxic condition, esmolol provides a measure of safety unavailable with other β blockers, because of the capability for rapid reversal of its β-blocking action if congestive heart failure or bronchospasm supervene. Thus, esmolol would be very useful for the treatment of supraventricular tachyarrhythmias, i.e., PSVT or atrial fibrillation, that occur postoperatively, particularly after cardiac surgery. In paroxysmal atrial fibrillation or automatic atrial tachycardia that occurs in the setting of acute respiratory failure secondary to chronic obstructive pulmonary disease, esmolol could provide rate control or suppression of the arrhythmia while its plasma concentration could be titrated to minimize bronchospasm. Similarly, esmolol could be very useful in controlling paroxysmal atrial fibrillation or automatic atrial tachycardia associated with sepsis or an acute myocardial infarction in patients in whom myocardial depressant effects of β blockade are a concern. Finally, esmolol could be helpful in the therapy of Torsades des pointe secondary to drug or metabolically induced long QT syndrome.

Esmolol could also be particularly useful when short-term β-blocker intervention is indicated. Specifically, esmolol would be useful for acute drug testing in the clinical electrophysiologic laboratory when testing the efficacy of β blockers to control reentrant SVT. Esmolol would also be appropriate in the therapy of intraoperative supraventricular tachyarrhythmias associated with induction of anesthesia.

In summary, esmolol is a β-adrenergic blocking agent with typical electrophysiologic actions on sinus node and AV nodal function. Its intensity is comparable to that of other intravenous β blockers. Unlike the other β blockers, however, esmolol has a very rapid onset and reversal of its electrophysiologic effects, which makes it particularly suited for acute antiarrhythmic interventions to control arrhythmias in clinical situations where the risk of untoward effects of β blockade is high.

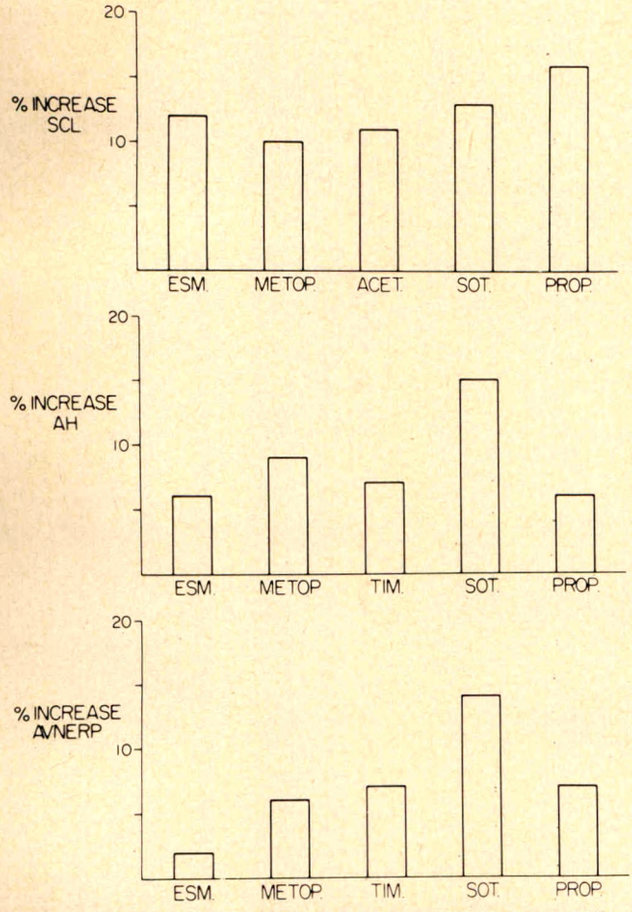

FIGURE 7. Effects of esmolol (ESM) are compared with those of other β blockers on sinus cycle length (SCL) **top,** AH interval **middle,** and AV nodal effective refractory period (AVNERP) **bottom,** as percentage increased with respect to control. Esmolol's effect on SCL and AH interval is generally comparable to those of the other β blockers, but its effect on AV nodal refractoriness is less pronounced. ACET = acebutolol; METOP = metoprolol; PROP = propranolol; SOT = sotalol; TIM = timolol.

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Discussion

Dr. Reves (Durham, North Carolina): Were any of the patients on digoxin or propranolol and, if so, have you any information about the interactions in terms of electrophysiologic effects of those 2 drugs?

Dr. Greenspan (Philadelphia, Pennsylvania): No, the patients were specifically not on digoxin or propranolol at the time, because we were going to be giving a β blocker and we were particularly careful about that. Only a few patients had some degree of left ventricular dysfunction, but they were not on either digoxin or propranolol.

Dr. Lowenthal (Philadelphia, Pennsylvania): Would you know whether there was any effect of esmolol on sinoatrial and atrioventricular function that mimes that of verapamil?

Dr. Greenspan: I have not specifically seen any data on this, but we know that verapamil has significant effects on atrioventricular nodal conduction time and atrioventricular nodal refractoriness, and it can have effects on sinus node function because of its calcium-blocking effect. In terms of comparable intensity, I think verapamil is probably significantly more effective in suppressing atrioventricular nodal conduction than are most of the β blockers. If one is going to address the question of the drug of choice in treating a patient who has paroxsymal supraventricular tachycardia and walks into the emergency room, I think there would be no doubt that, assuming there was no significant degree of left ventricular dysfunction, you would reach for verapamil first. However, in a patient in the hospital, where high catecholamine tone is going to be an important inciting factor in these arrhythmias, one should give consideration to esmolol. I have seen β blockers work better for postoperative atrial fibrillation, particularly after cardiac surgery, than digoxin or other interventions that might have more intense atrioventricular nodal blocking effect, because of the specific effects of β blockers on sympathetic tone.

Dr. Iskandrian (Philadelphia, Pennsylvania): What was the duration of the infusion? In atrial fibrillation, does esmolol slow the rate, or does it convert it to sinus rhythm?

Dr. Greenspan: The second question probably should be directed to Dr. Morganroth, who is going to be presenting data specifically on that. Esmolol does convert atrial fibrillation in some cases, although the major effect was that esmolol slows the heart rate rather significantly and in a fashion comparable to propranolol. As far as the duration of our infusion, it varied depending upon the duration of time it took to make the electrophysiologic measurements, but on average we started making the measurements at 10 minutes of the maintenance infusion, and it took about 18 to 20 minutes. So the total duration of the maintenance infusion was about 30 minutes. There is some degree of variability in making these electrophysiologic measurements if the patient does not cooperate in terms of showing us a good His potential. We have to reposition catheters and so on and that can create some problems with the duration of the measurements.

Dr. Laddu (McGaw Park, Illinois): In the figure showing the heart rate effect over baseline, clearly there was a significant decrease in the heart rate in the esmolol infusion. Then when esmolol was discontinued, the heart rate slipped back so much that there was an overshoot beyond baseline. I find that very interesting because in some of our studies where we gave the drug for half an hour, 4 hours or even 24 hours continuously in patients with supraventricular tachycardia, we did not see that feature. There was no overshoot, and heart rates at the end of the infusion were at the level of the baseline or slightly lower. How would you account for that difference?

Dr. Greenspan: I would invoke Dr. Gray's caveat that we have to consider what the clinical situation is when we are talking about the response of this drug. Patients with supraventricular tachycardia have their catecholamine levels significantly raised because they have to combat the rather rapid rate and shortened filling time to maintain normal cardiac output. When you stop the drug, there may be differences in the response time than if you have a patient in whom you have just been doing some pacing and has not necessarily been in supraventricular tachycardia for a long time. Again, our study patients were in the electrophysiologic laboratory, being instrumented in a relatively unphysiologic situation compared with normal volunteers who just have intravenous lines in place. That might make a difference in the general level of their sympathetic tone. Also, of course, their underlying left ventricular function would make a difference. So, I am not sure that we should expect to see exactly the same kind of responses in our patient group as in either of the other 2 treatment groups that you have talked about.

Dr. Laddu: One possibility is that your patients who are going for electrophysiologic testing are on sedatives, and perhaps by the time you are going for the post-esmolol effect, the sedative is wearing off.

Dr. Greenspan: I think that is a very good point and it bears looking into. There are two things we can do. We can go back and look at our patients to determine what additional medications were given, and when. We can look to see where the diazepam was given and whether or not it was discontinued later in the study. We can also get an idea of how the patients were responding as there were comments made in those charts about how comfortable a patient was. The other thing we can do is to look at that prospectively in a new group of patients, i.e., just look at cycle length and heart rate at the beginning and the end of the electrophysiologic study, and see if there is a significant effect there. Clearly, the patients are more uncomfortable at the end of the procedure after lying flat for 2 to 3 hours.

Dr. Sonnenblick (Bronx, New York): But the effects were relatively small and you did not have a masked tachycardia occurring on anybody. I think it is important not to worry just about the averages, but also the extent and whether there were exceptions. Did you find anybody with the type of overshoot that might be detrimental?

Dr. Greenspan: No, actually not. It was pretty uniform. The standard deviations are not large and virtually all of the

patients showed small reversal of the effect. I would not be concerned about that clinically.

Dr. Sonnenblick: The other thing you might consider is that it is probably unfair to say that the onset of action is 5 minutes when the first measurement was made at 5 minutes.

Dr. Greenspan: Absolutely. That point is very well taken. I think if I were to do the study over again I would start sampling much earlier on because the onset appears to be sooner than 5 minutes.

Dr. Lee (McGaw Park, Illinois): Your comparative figure with esmolol and the other β blockers showed that the effects of esmolol were comparable, with the exception of the atrioventricular nodal effective refractoriness. Given the fact that in atrial flutter and fibrillation, you get comparable lowering of ventricular rate, do you see any clinical significance in the fact that esmolol doesn't lower atrioventricular nodal effective refractory period?

Dr. Greenspan: It is sometimes very, very hard to extrapolate from the changes that one sees in the electrophysiology laboratory when making static measurements of the atrioventricular nodal function in one clinical situation to situations of arrhythmias. Here, you are looking at the AH interval during sinus rhythm and then at a rate of 100 beats/min. If one then looks at the effect of that drug in someone who is in paroxysmal atrial fibrillation or supraventricular tachycardia at 160 or 180 beats/min, I think we might unmask more intense effects. One could look at that effect by pacing faster and seeing if one uncovers a stronger effect. I think that is one of the reasons why we do not see much of an effect in the static measurement of atrioventricular nodal refractoriness, and yet it can have significant effects on the clinical situation. Therefore, if one looks at measurements of other antiarrhythmic effects, such as those of the membrane-active antiarrhythmic agents on ventricular refractoriness or conduction, one would be hard pressed to see a correlation between that and some of the very intense effects in terms of suppressing ventricular tachyarrhythmias.

Effects of Esmolol on Cardiac Function: Evaluation by Noninvasive Techniques

ABDULMASSIH S. ISKANDRIAN, MD, A-HAMID HAKKI, MD, and ATUL LADDU, MD

In a double-blind, randomized, crossover study, the effects of esmolol and propranolol were examined at rest and during peak upright exercise in 15 patients. At rest, both esmolol and propranolol significantly decreased heart rate, systolic blood pressure, rate-pressure product, left ventricular ejection fraction, cardiac index and right ventricular ejection fraction. During exercise, significant decreases were also found in heart rate, systolic blood pressure and cardiac index in both treatment groups. No significant differences were found between mean esmolol and mean propranolol measurements at rest and during exercise, except for the exercise systolic blood pressure, which was lower during esmolol infusion. Blood levels of esmolol decreased markedly by 30 minutes postinfusion, as did its β-blocking action. Esmolol was well tolerated with no important local, systemic or laboratory abnormalities. Thus, the effects of esmolol on cardiovascular performance at rest and during exercise are similar to those of propranolol.

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Beta-adrenoceptor blocking drugs differ considerably in pharmacodynamic and pharmacokinetic properties. In recent years considerable attention has been given to such properties as cardioselectivity and intrinsic sympathomimetic activity. Propranolol, a nonselective β-adrenergic blocking agent without intrinsic agonistic activity, has been shown to decrease heart rate, systolic blood pressure and cardiac output, and to increase left ventricular (LV) filling pressure and systemic vascular resistance.[1] Its effects on LV ejection fraction (EF) have been evaluated in normal subjects both at rest and during exercise. These reports indicate that propranolol decreases LVEF at rest and blunts the exercise-induced increase in EF expected in normal subjects.[2–4] In patients with coronary artery disease, propranolol at rest produced either no change or a decrease in LVEF.[5] However, in these patients during exercise, propranolol has been shown to either increase[6,7] or produce no change[8,9] in EF. Therefore, in patients who have exercise-induced myocardial ischemia, β-adrenergic blockers may, by decreasing myocardial oxygen demand, decrease or prevent the development of ischemia and, hence, improve the EF.

Currently available β blockers have a relatively long duration of action and thus must be used with caution in patients who cannot tolerate β blockade due to the presence of such contraindications as history of congestive heart failure and chronic obstructive lung disease. Ideally, a β blocker with an ultrashort half-life whose action could be terminated rapidly if needed is desirable in these patients. Esmolol, a cardioselective β blocker with no intrinsic sympathomimetic activity, has been shown to be ultrashort-acting with a 9 minute half-life.[10]

This report compares the effects of esmolol with those of propranolol, at equipotent β-blocking doses, on cardiovascular performance in patients evaluated by noninvasive techniques.

Materials and Methods

The hemodynamic effects of esmolol were compared with those of propranolol in a double-blind, randomized, crossover study. The study drug sequence was determined using a computerized randomization schedule. The investigator remained blinded throughout the study as to which study drug was administered on the 2 drug study days. Blinding was achieved by having concurrent infusions and injections on the drug days. Esmolol was administered using an infusion schedule and propranolol was administered by an injection schedule. However, on each drug study day, only 1 of the treatments contained an assigned study drug while the other contained a matching placebo. The study consisted of 3 study days, each separated by at least 48 hours from the preceding study day. The first day was for the baseline study. On the remaining 2 study days, the patients received an esmolol infusion on 1 day and propranolol on the other according to the order specified in the randomization schedule. On the baseline study day, each patient underwent a 30- to 45-minute stabilization period followed by radionuclide angiography at rest and during peak upright exercise.

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TABLE I Summary of Hemodynamic Data Obtained in 15 Patients

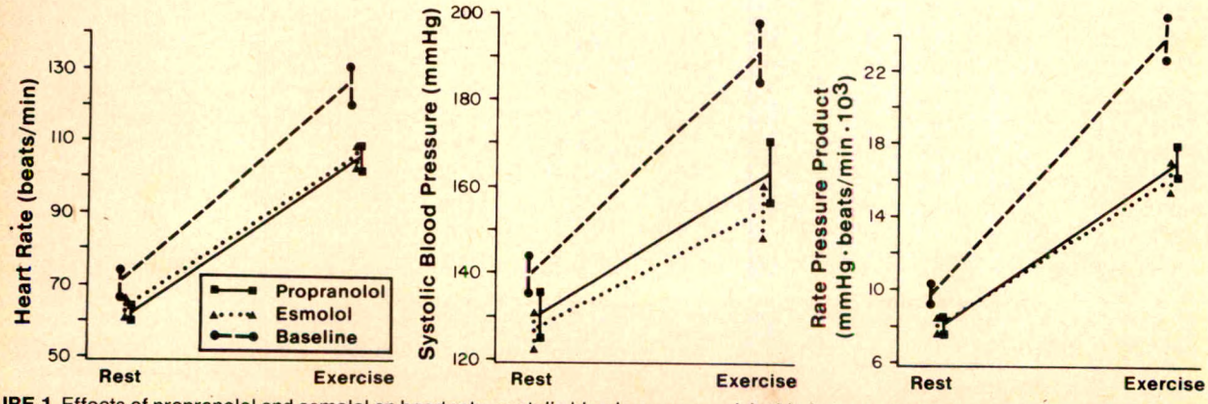
	Baseline (B)		Esmolol (E)		Propranolol (P)		Significance Among Treatments#	
	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex
HR (beats/min)	70 ± 4	126 ± 5	64 ± 2	106 ± 3	62 ± 2	106 ± 4	B>E,P	B>E,P
SBP (mm Hg)	139 ± 5	191 ± 7	127 ± 4	155 ± 6	130 ± 5	163 ± 7	B>E,P	B>P>E
DBP (mm Hg)	90 ± 3	94 ± 4	87 ± 3	93 ± 3	87 ± 3	93 ± 3	NS	NS
RPP	10 ± 1	24 ± 1	8 ± 0	16 ± 1	8 ± 0	17 ± 1	B>E,P	B>E,P
LVEF (%)	51 ± 5	53 ± 4	42 ± 4	49 ± 4	45 ± 4	51 ± 4	B>E,P	NS
RVEF (%)	44 ± 2	50 ± 2	36 ± 1	43 ± 2	37 ± 2	45 ± 2	B>E,P	B>E,P
LVEDV index (ml/m^2)	95 ± 11	112 ± 11	102 ± 11	111 ± 10	97 ± 9	111 ± 11	NS	NS
LVESV index (ml/m^2)	52 ± 11	59 ± 11	64 ± 12	63 ± 11	58 ± 9	60 ± 11	E>B	NS
CI (liter/min/m^2)	2.9 ± 0.2	6.6 ± 0.3	2.4 ± 0.1	5.2 ± 0.3	2.4 ± 0.1	5.3 ± 0.3	B>E,P	B>E,P
PTT (s)	6 ± 0.3	3.2 ± 0.2	6.8 ± 0.3	4.6 ± 0.3	7.7 ± 0.4	4.4 ± 0.4	P>B	E,P>B
PBV (liter)	0.6 ± 0.0	0.7 ± 0.0	0.5 ± 0.1	0.8 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	NS	NS
SBP/ESV index	1.1 ± 0.2	1.2 ± 0.2	0.7 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.1 ± 0.2	B>E,P	B>E
WMS	10 ± 1	9 ± 1	8 ± 1	9 ± 1	9 ± 1	10 ± 1	B>E	NS
Ex WI		430 ± 30		430 ± 30		430 ± 30		NS
Ex duration		7 ± 1		7 ± 1		7 ± 1		NS

Results are expressed as mean ± standard error of the mean. # probability value (p) < 0.05 was considered significant.
CI = cardiac index; DBP = diastolic blood pressure; Ex = exercise; HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NS = no significant difference between treatments (p >0.5); PBV = pulmonary blood volume; PTT = pulmonary transit time; RPP = rate-pressure product; RVEF = right ventricular ejection fraction; SBP = systolic blood pressure; WI = workload; WMS = wall motion score.

On drug treatment days, study drugs were administered after a 30- to 35-minute stabilization period. The esmolol infusion schedule required a 2-minute loading infusion at a rate of 500 μg/kg/min, followed by a constant infusion rate of 200 μg/kg/min (esmolol was diluted in normal saline to achieve a final concentration of 10 mg/ml), which was continued until both the rest and exercise radionuclide angiograms were completed. Propranolol was administered as four 1-mg injections, each of which was administered over 1 minute. At approximately 12 minutes after initiation of study drug, each patient underwent radionuclide angiography at rest and during peak exercise. The heart rate and blood pressure were recorded every 2 minutes during infusion and every 5 minutes for 30 minutes after the end of infusion on both study days. Blood samples for esmolol levels were collected at rest approximately 12 minutes after the start of infusion, during peak exercise and at 30 minutes postinfusion. Safety data consisting of blood chemistry, hematology and urinalysis were evaluated on the baseline day and 30 minutes postinfusion on both drug study days.

There were 15 patients in this study, 12 men and 3 women between the ages of 45 and 66 years. These patients were being evaluated by exercise testing for anginal symptoms.

The radionuclide angiograms were performed with the first-pass method using a computerized multicrystal camera (Baird-Atomic, System-77). The resting studies were performed while the patient was seated in the upright position on the bicycle ergometer and the exercise studies were performed during peak upright exercise. On the baseline day a symptom-limited, upright exercise was performed and exercise was terminated when the patient had excessive fatigue, leg weakness or chest pain. From the exercise data on the baseline day, workload and exercise duration were determined for each patient, and during the subsequent 2 drug study days, the exercise was terminated at precisely the same exercise workload and duration that was achieved during the baseline day. During exercise and recovery, 3 electrocardiographic leads (II, V_5 and aVF) were constantly monitored. The radionuclide angiograms were processed with the software incorporated into the multicrystal camera. The following data were obtained from the radionuclide angiograms: LVEF, LV end-diastolic volume, end-systolic volume, stroke volume, cardiac output, mean pulmonary transit time, pulmonary blood volume and right ventricular (RV) EF. LV wall motion was assessed in 3 segments—anterior, apical and inferior—and each segment was assessed on a



GURE 1. Effects of propranolol and esmolol on heart rate, systolic blood pressure and double (rate pressure) product at rest and during exercise. esults are expressed as mean ± standard error of the mean for 15 patients. Both esmolol and propranolol significantly lowered the heart rate, systolic blood pressure and double product at rest and during exercise.

scale of 0 to 4: 4 = normal motion, 3 = mild hypokinesia, 2 = moderate hypokinesia, 1 = severe hypokinesia and 0 = akinesia or dyskinesia. The methods of measuring the various radionuclide descriptors and their reproducibility and correlation with other measurements obtained during cardiac catheterization have been described in detail from this and other laboratories.[11,12]

Results

Eight patients received esmolol on the first drug study day and propranolol on the crossover day; 7 patients received propranolol on the first drug study day and esmolol on the crossover day. There were no adverse local or systemic reactions and no clinically important laboratory changes.

The hemodynamic data at rest and during exercise in the baseline study day and the 2 drug study days are shown in Table I and in Figures 1, 2 and 3. At rest, significant drug effects were found in a number of these measurements; the most important were the heart rate, systolic blood pressure, rate-pressure product, LVEF, RVEF, cardiac index and systolic blood pressure to end-systolic volume ratio. The control measurements were significantly higher than esmolol and propranolol measurements, but no significant differences were found between the average esmolol and the average propranolol effects.

Similarly, during peak exercise, significant treatment effects were found for the heart rate, systolic blood pressure, rate-pressure product, cardiac index, RVEF and mean pulmonary transit time. It should be noted that the RVEF was measured in only 12 patients. In the remaining 3 patients, the RV images were not totally contained in the gamma camera's field of view and therefore the RVEF could not be measured reliably. The average baseline measurements were significantly higher than both the average esmolol and the average propranolol measurements except in pulmonary transit time. Also, with the exception of the exercise systolic blood pressure (esmolol, 155 mm Hg; propranolol, 163 mm Hg), no significant differences were found between esmolol and propranolol in the measurements just described (Table I). There was no significant treatment effect on exercise LVEF, end-diastolic or end-systolic volumes. The hemodynamic changes at rest and exercise were similar among patients with resting baseline LVEF ≥50% (n = 10) and among patients with resting baseline EF of <50% (n = 5).

TABLE II Blood Levels of Esmolol and Its Inactive Metabolite ASL-8123* (mean ± standard error of the mean)

Study	Pts (n)	Infusion	30 Minutes Postinfusion
Esmolol	7	0.59 ± 0.07	0.01 ± 0.01
ASL-8123 (μg/ml)	7	2.20 ± 0.20	8.55 ± 0.50

*Blood levels were not available on all patients. The relative potency of metabolite is 1/320th of the parent compound.

This study was not designed to compare the effect of esmolol and propranolol on exercise-induced ischemic changes. However, the data show that the incidence of ST-segment changes and arrhythmias was greatly reduced in both treatment groups compared with the baseline period. These changes did not reach significance, probably owing to the small sample size.

Because of its rapid metabolism, esmolol blood levels decreased from 0.59 ± 0.07 μg/ml during infusion to 0.01 ± 0.01 μg/ml at 30 minutes postinfusion. The blood level of the inactive metabolite ASL-8123 (1/320th the potency of esmolol) continued to increase up through the final sampling time. These results are comparable to those obtained in the open-label study with invasive hemodynamic monitoring (Table II).

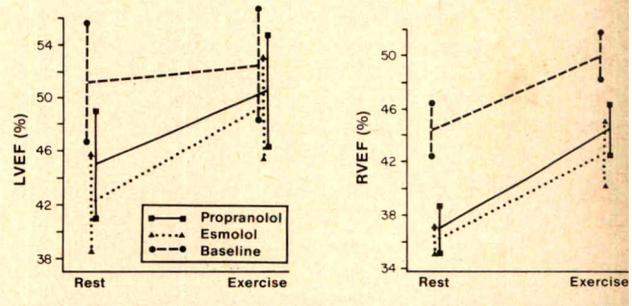


FIGURE 2. Effects of esmolol and propranolol on rest and exercise left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF).

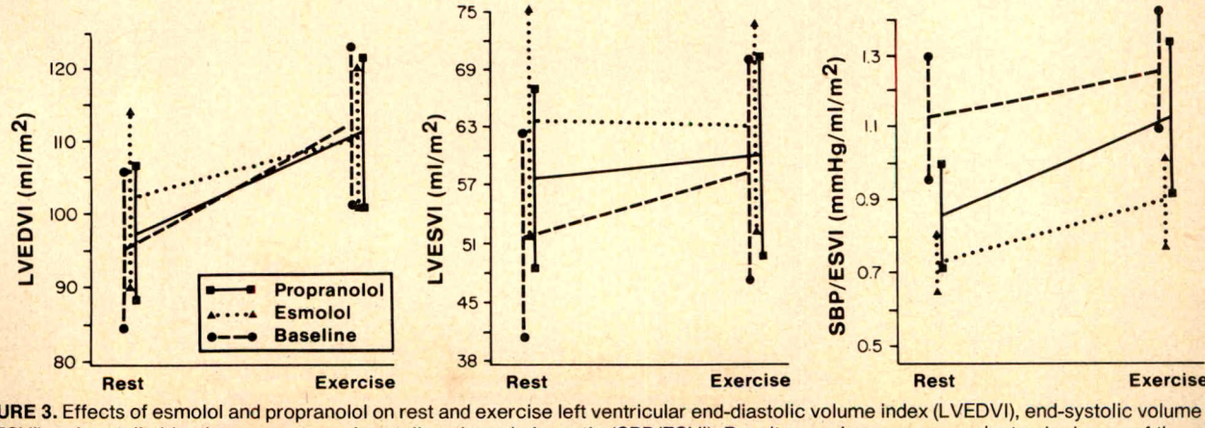


FIGURE 3. Effects of esmolol and propranolol on rest and exercise left ventricular end-diastolic volume index (LVEDVI), end-systolic volume index (LVESVI) and systolic blood pressure-to-end-systolic volume index ratio (SBP/ESVI). Results are shown as mean ± standard error of the mean.

Discussion

Esmolol, when given intravenously, produces hemodynamic changes typical of β-adrenergic blockade.[1] These changes are rapidly reversed upon discontinuation of infusion consistent with the short half-life of esmolol.[10,13] In this double-blind, randomized, crossover study, the hemodynamic effects of esmolol were very similar in magnitude and direction to those of intravenous propranolol.[13] At rest, esmolol, like propranolol, produced a decrease in heart rate, systemic pressure, cardiac index and stroke work index. There was a modest but statistically significant depression in LV function characterized by a decrease in EF and an increase in LV filling pressure and end-systolic volume. Esmolol and propranolol also decreased the resting RVEF. During exercise, esmolol produced a decrease in heart rate, systemic pressure, cardiac index and RVEF. Once again, the changes during exercise were similar to those produced by propranolol. Neither esmolol nor propranolol had significant effects on exercise LVEF, end-diastolic volume and end-systolic volume.[13] Esmolol up to a dose of 300 μg/kg/min was well tolerated with no adverse local or systemic effects.

The hemodynamic effects of β-blocking agents (decreased heart rate, blood pressure, cardiac index and stroke work index) typically result in decreased oxygen consumption by the myocardium, and thereby have a beneficial effect in the therapy of ischemic heart disease.[14–16] The accompanying modest depression of LV function characterized by a decrease in LVEF could become a problem in treating the sensitive patient with acute ischemic heart disease (acute myocardial infarction or unstable angina pectoris). Esmolol, because of its short half-life, may offer a safer alternative to such long-acting β blockers as propranolol in these acute settings. Should dangerous adverse effects occur, they could be readily reversed by termination of the infusion. Further studies are in progress to evaluate the hemodynamics and safety of esmolol in patients with depressed LV performance. Pending the outcome of those studies, esmolol may be the β-blocking agent of choice in the treatment of patients with acute myocardial infarction.

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Discussion

Dr. Gray (Los Angeles, California): To better understand the type of patients in your radionuclide study, I assume they were being evaluated prospectively for ischemic heart disease. I would gather from their ejection fraction response that this was not the ultimate diagnosis in all patients. Their resting ejection fractions were in the borderline-to-normal range, but the response to exercise was, by and large, about the same as control measurements. It did not look like there was a significant drop in ejection fraction with exercise in the control state. I would like to understand better the substrate upon which the 2 β blockers were used.

Dr. Iskandrian (Philadelphia, Pennsylvania): By and large, they were patients who had typical or atypical angina pectoris. Ten of the 15 patients had resting ejection fractions within the normal range for our laboratory—that is, about 50%. The other 5 had abnormal resting ejection fractions; all but 1 were in the low 40% range. Our second patient had an ejection fraction of 18% at rest, and he tolerated esmolol well. The response, by and large, is typical of patients with coronary artery disease; the ejection fraction did not increase with exercise, their end-systolic volume increased and they had either rest or exercise wall motion abnormalities. Diagnosis of 6 patients was confirmed either by infarction or by coronary angiogram, but the remaining 9 patients were clinically determined to have coronary heart disease.

Dr. Sonnenblick (Bronx, New York): I think it would be advantageous to show all the data. Without the discrete data points, it is like the 3 fellows who go hunting and one shoots high and the other shoots low and the third fellow says, "You got him." One would like to know if the averages reflect or mask variations in the data.

Dr. Morganroth (Philadelphia, Pennsylvania): In that regard, was there a difference between the response you observed in the single patient with 18% versus the patients with lower than normal ejection fractions?

Dr. Iskandrian: Actually we did analyze them. Let me answer Dr. Sonnenblick's question first. The whole of the individual data points are in the May 1985 issue of *The American Journal of Cardiology* and you can see them. All the data are there: patient by patient and what happened to them during both studies at rest and during exercise. We analyzed the studies in the 10 patients who had normal ejection fractions at rest and the 5 who were abnormal, and there was no significant change between the response in the 2 groups. But, mind you, of the patients with the abnormal ejection fraction, 4 of the 5 were mildly abnormal. In patients with a severe dysfunction, it may be a different issue. We are now in the process of looking at such patients, and it indeed looks like the responses might be different from the mild dysfunction.

Dr. Morganroth: In what regard?

Dr. Iskandrian: We are seeing more left ventricular dilation with the infusion of esmolol, which is something of concern if you start thinking of the myocardial oxygen demand in relation to wall stress and so on.

Dr. Morganroth: Those changes might also be different, of course, with the underlying etiology. For example, when you exercise the patient with ischemic heart disease, the β-blocking effect in ischemia may be different than if there is no coronary ischemia, such as in a patient with idiopathic cardiomyopathy. You do not have a large enough number, obviously, to look at the etiologic, mechanistic and absolute levels of ejection fraction.

Dr. Iskandrian: That is a very important point. Any evaluation of a β blocker during exercise is dependent on the patient population and the exercise protocol. It is completely different if you exercise a patient with coronary disease and during peak exercise that patient becomes ischemic, because you hope that the β blocker will decrease the double product and at the same workload he won't be ischemic. If the patient wasn't ischemic, then β-blocker response is going to be different. Mean differences sometimes hide a lot of variance beween individuals.

Dr. Gray: Is it your feeling that, in the patients with documented ischemic heart disease, esmolol or propranolol is protective of exercise-induced ischemia based on hemodynamic, clinical or electrocardiographic response?

Dr. Iskandrian: I think there is no question that β blockade is protective if that patient develops ischemia during the control measurement and if that patient is going to do the same exercise with the medication. However, if you exercise patients longer while they are on a β blocker, they may become just as ischemic as without medication.

Dr. Sonnenblick: I think what Dr. Iskandrian is saying is that with the limitation of cardiac output that they have, they may be limited in their exercise performance for noncardiac reasons. So, the problem is much more complex than the usual simple picture that was once presented.

Dr. Lowenthal (Philadelphia, Pennsylvania): Often, people on the conventional oral β blockers developed skeletal muscle fatigue during exercise, possibly related to some blunting of lipolysis and also to the decrease in cardiac output. Did you notice if this effect was also present during the esmolol component? Did they develop any lower extremity fatigue?

Dr. Iskandrian: Not really. Clinically, they tolerated it, and with most patients we stopped them when they were on the drug because we had reached our predetermined endpoint with no symptoms related to muscle fatigue.

Dr. Laddu (McGaw Park, Illinois): Esmolol was given only for a short period. Isn't the onset of fatigue a long-term effect of β blockade?

Dr. Iskandrian: That may be true, but at rest I think I suggested it in something I wrote about 5 years ago. I said that if you put patients with sick hearts on chronic β-blocker care, and they exercise, the ejection fraction is not going to be better. If the heart rate is also limited, then the cardiac output will be limited and this is why they feel so tired and have some noncardiac symptoms.

Dr. Greenspan (Philadelphia, Pennsylvania): Dr. Iskandrian, I am very fascinated by the observation that there were some differential responses in the right ventricle and the left ventricle, in terms of ejection fraction, to the β blockade. You say you have some thoughts about it and I would like to hear them. Do you think there may be geometric factors that play a role in terms of differences in the right ventricular and left ventricular response?

Dr. Iskandrian: I think that might be, but it might also be that the β receptors in the right ventricle are different in quality or quantity from those in the left ventricle. It might also be that you are dealing with an afterloading tendency. We saw from the hemodynamic changes, despite no change in end-diastolic volume, that wedge pressure and pulmonary artery pressure are increased. I think that even with exercise, these changes might not be due primarily to changing contractility of the right ventricle but to an afterload-dependent phenomenon secondary to decreased left ventricular contractility.

Dr. Gray: Actually, we did look at this somewhat tangentially, if you will, in a hypertensive study in the postcardiac surgical patient. We found the left ventricular stroke work index did decrease somewhat with esmolol. Although not tremendous, statistically significant decreases were seen with esmolol. The right ventricular stroke work index, by contrast, decreases minimally and nonsignificantly, and the main difference seems to be in the afterload effects. In other words, the work demand on the right heart is still greater. The effect of giving esmolol in contrast to, say, nitroprusside, is that the pulmonary artery systolic pressure does go up a bit more than, say, the afterload on the left side.

Dr. Sonnenblick: I agree with that.

Dr. Gray: So what is demanded of the left heart is different, and I presume catecholamines or some other hemodynamic response, reflex or otherwise, are going to be different from right to left.

Dr. Sonnenblick: I think the bottom line is how well esmolol is tolerated in this broad group of patients. I think it is very easy to make a great deal out of the changes in the ejection fraction, but there is sympathetic withdrawal there. Also, if the cardiac output and the stroke volume are decreasing, or just the stroke volume is, the ejection fraction will tend to decline on its own. In other words, ejection fraction will fall as cardiac output falls. Ejection fraction does not remain a direct indicator of contractility in that circumstance—directionally, it is probably correct, but it is not directly proportional and it is remarkably well tolerated. What you are also pointing out is there were no broad exceptions.

Dr. Iskandrian: Yes, that is true.

Comparative Efficacy and Tolerance of Esmolol to Propranolol for Control of Supraventricular Tachyarrhythmia

JOEL MORGANROTH, MD, LEONARD N. HOROWITZ, MD, JEFFREY ANDERSON, MD, PRASAD TURLAPATY, PhD, and the ESMOLOL RESEARCH GROUP*

This multicenter, double-blind, randomized, parallel study compared the effectiveness and tolerance of intravenous esmolol with intravenous propranolol in patients with supraventricular tachyarrhythmia (heart rate [HR] >120 beats/min). Efficacy was evaluated in 53 patients receiving esmolol and in 57 patients receiving propranolol. Patients randomized to esmolol received infusions of various doses of esmolol ranging from 50 to 300 μg/kg/min (each dose infused for 5 minutes) over a 30-minute titration period with intermittent placebo boluses of propranolol. Those randomized for propranolol received 1 mg/min for the first 3 minutes, and then another 3 mg from minutes 5 to 8 with continuous placebo esmolol infusion during the 30-minute titration period. A therapeutic response, defined by 20% or greater reduction in HR, HR <100 beats/min or conversion to normal sinus rhythm, was achieved in 72% of patients on esmolol compared with 69% of patients on propranolol (difference not significant). The therapeutic response was maintained in 67% of patients on esmolol and 58% of patients on propranolol (difference not significant) during a 4-hour maintenance period. Conversion to normal sinus rhythm occurred in 14% of esmolol patients and 16% of propranolol patients during titration and 10% of esmolol and 8% of propranolol patients during maintenance. After discontinuation of study drugs, a more rapid reversal of the reduction in HR was observed in esmolol patients compared with those patients receiving propranolol. Adverse reactions were seen in 29 (45%) patients on esmolol and 11 (18%) patients on propranolol. The principle adverse reaction was hypotension, which was predominantly asymptomatic and found in 23 patients receiving esmolol and 4 receiving propranolol. Hypotension resolved quickly after discontinuation of esmolol and did not cause any significant consequences.

This study demonstrates that esmolol is comparable in safety and efficacy to propranolol, and unlike propranolol, it has a much faster termination of β blocking because of its short half-life. Esmolol, therefore, has marked theoretical advantages in its use in the intensive care unit for the control of supraventricular tachyarrhythmia.

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Beta-adrenergic blocking drugs have been standard therapy for the treatment of acute ischemic, hypertensive and tachyarrhythmic states.[1] In the intensive care unit, intravenous β blockers can provide for a rapid correction of unstable cardiovascular conditions; however, their use also involves such potential risks as serious adverse reactions including excessive bradycardia, heart block and worsening of left ventricular dysfunction. These adverse reactions usually dissipate slowly, which may restrict the use of currently available β blockers whose elimination half-lives range from 2 to 6 hours.[2] Ideally, a β blocker with an ultrashort half-life whose action could be terminated rapidly if needed is desirable in acute settings.

Esmolol, a cardioselective β blocker with no intrinsic sympathomimetic activity, has been shown to be ultrashort-acting with a 9.2-minute half-life.[3] This report details a double-blind, randomized, controlled trial that compared the efficacy and tolerance of esmolol with propranolol, both administered intravenously,

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TABLE I Prestudy Variables in Baseline Comparative Patients Used for Efficacy Analysis

	Esmolol (n = 53)	Propranolol (n = 57)
Age (years)	65 ± 11	63 ± 10
Men	33 (62%)	35 (61%)
Heart rate (beats/min)	147 ± 16	146 ± 18
Systolic blood pressure (mm Hg)	126 ± 22	118 ± 15
Diastolic blood pressure (mm Hg)	78 ± 11	73 ± 11
Postoperative	27 (51%)	28 (49%)
Coronary artery disease	16 (30%)	18 (32%)
Type of SVT		
Atrial fibrillation	40 (75%)	48 (84%)
Atrial flutter	9 (17%)	8 (14%)
Automatic atrial tachycardia	3 (6%)	0
Sinus tachycardia	1 (2%)	1 (2%)

SVT = supraventricular tachyarrhythmia.

TABLE II Types of Therapeutic Response in Patients Used for Efficacy Analysis

Study Period Response	Efficacy Patients: Esmolol	Efficacy Patients: Propranolol
Entered titration period	50	55
Achieved therapeutic response*†	36 (72%)	38 (69%)
Type of therapeutic response†		
> 20% HR reduction	32 (64%)	38 (69%)
HR < 100 beats/min	16 (32%)	19 (34%)
Conversion to NSR	7 (14%)	9 (16%)
Entered maintenance period	30	36
Maintained therapeutic response*†	20 (67%)	21 (58%)
Type of therapeutic response‡		
> 20% HR reduction	20 (67%)	18 (50%)
HR < 100 beats/min	13 (43%)	15 (42%)
Maintained NSR	5 (17%)	8 (22%)
Converted to NSR	3 (10%)	3 (8%)

HR = heart rate; NSR = normal sinus rhythm.
* A patient may achieve more than 1 type of therapeutic response.
† Denominator for percentage response equals number of efficacy patients who had entered titration period.
‡ Denominator for percentage response equals number of efficacy patients who had a therapeutic response during titration and entered the maintenance period.

to control excessive tachycardia in patients with supraventricular tachyarrhythmias (SVTs).

Methods

This study was conducted in 12 centers in the U.S. using a common protocol. Patients' inclusion criteria were age older than 18 years and heart rate (HR) >120 beats/min owing to SVT. Supraventricular tachyarrhythmias were defined as the presence of atrial fibrillation, atrial flutter, ectopic atrial tachycardia or sinus tachycardia of cardiac origin. Patients with preexcitation syndromes were excluded. Other exclusions included uncontrolled congestive heart failure or hypotension (<100/70 mm Hg), ventricular arrhythmias requiring acute therapy, severe disorders of impulse conduction, such as sick sinus syndrome, atrioventricular block and tachycardia due to an external condition, such as anemia or infection. Patients with electrolyte imbalance, chronic obstructive pulmonary disease, asthma that precluded β blockade or prior allergy to a β blocker were also excluded. Patients who had been on monoamine oxidase inhibitors or catecholamine-depleting agents, such as reserpine, within 6 weeks or those who had taken a β- or calcium-channel blocker within 2 half-lives of entry to the study were also excluded. Women were permitted entry if they were not pregnant.

Protocol: If patients demonstrated SVT with HR >120 beats/min for a minimum of 30 minutes (baseline period), they were randomly assigned to either an infusion of esmolol with placebo injections of propranolol or propranolol injection with placebo esmolol infusion. Esmolol was titrated upward according to patient response over 30 minutes during the titration period. Six different levels of esmolol dosing were used, each over 5 minutes. During the first minute of each of the 5-minute periods, esmolol was infused with a loading dose (500 μg/kg/min) and then for the succeeding 4 minutes, esmolol was titrated from 50, 100, 150, 200, 250 and finally to 300 μg/kg/min. Intravenous boluses of active propranolol were administered depending on patient response, in 1-mg doses over 1 minute for the first 3 minutes and then from minutes 5 to 8, thus providing 6 boluses or 6 mg of active propranolol.

During the titration period, all patients simultaneously received either active esmolol infusion and placebo propranolol injection or active propranolol injections with placebo esmolol infusion to ensure the double-blind status. Infusions were controlled with the use of a volumetric pump, which

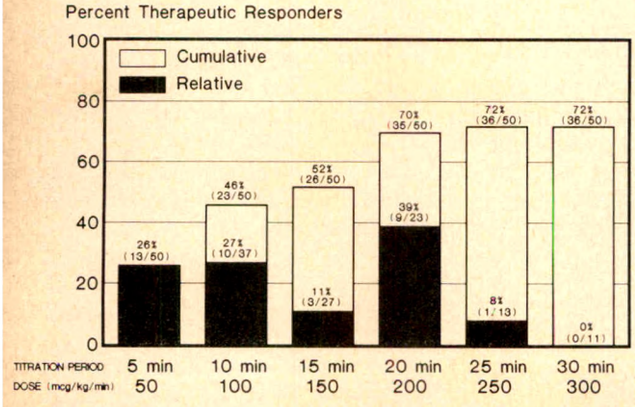

FIGURE 1. Percentage of efficacy patients achieving a therapeutic response during the titration period, by esmolol dosage. Cumulative percent is the number of responders at a given dosage or lower divided by the number of efficacy patients (n = 50). Relative percent is the number of responders at a given dosage divided by the number of efficacy patients treated with that dosage.

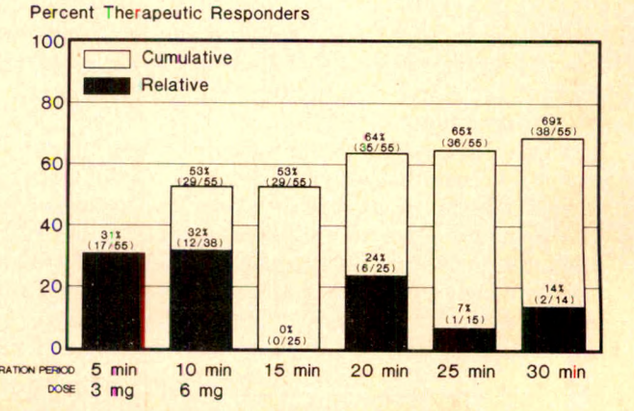

FIGURE 2. Percentage of efficacy patients achieving a therapeutic response during the titration period, by propranolol dosage. Cumulative percent is the number of responders at a given dosage or lower divided by the number of efficacy patients (n = 55). Relative percent is the number of responders at a given dosage divided by the number of efficacy patients treated with that dosage.

was standardized and calibrated at each of the 12 clinical study centers.

The therapeutic endpoints used in this study were a >20% reduction in ventricular rate compared with the average initial 30-minute baseline HR, a reduction in absolute ventricular rate to <100/min or a conversion to normal sinus rhythm.

Upon reaching a therapeutic endpoint, the patient then entered a 4-hour maintenance period using the dose infusion level at the time that the therapeutic endpoint was achieved. At the discretion of the investigator, patients not responding during titration were either entered into the 4-hour maintenance period or terminated from the study. After the maintenance period, the patients had their infusions discontinued and a 20-minute follow-up period was used to profile clinical evaluations.

Before study, data from the patient's history, physical examination, 12-lead electrocardiogram and routine laboratory analyses were recorded and these were repeated within 24 hours of the follow-up period. Blood pressure and HR were obtained every 10 minutes during the baseline period, every 5 minutes during titration, every 20 minutes during the maintenance and every 10 minutes during the follow-up period. Heart rates were determined by hand counting a 1-minute electrocardiogram rhythm strip (lead II) at each of these intervals.

Statistical analysis: A 2-way analysis of variance was used to test for differences among centers for all variables as well as differences in recruitment. Tests for center and treatment interaction effects were performed using a standard log-linear model for proportions. Two-way analysis of variance for continuous variables and a log-linear model for categorical data were used for response variables and within group comparisons were performed using the paired *t* test. Significance was defined at the 0.05 level before 2-tailed hypothesis.

Results

Enrollment and demographics: Of the 127 patients who were entered into the protocol and received 1 of the study drugs, 11 patients on esmolol and 6 on propranolol were disqualified from the efficacy analysis because of protocol deviations. Safety data will be, therefore, reported on 64 esmolol and 63 propranolol patients, whereas efficacy data will be reported on 53 esmolol and 57 propranolol patients. Efficacy data in regard to HR reduction will be reported on 50 esmolol and 55 propranolol patients because 3 patients receiving esmolol and 2 patients receiving propranolol were excluded because of investigator error in judging therapeutic endpoint.

There was no difference among the demographic and clinical characteristics of the patients randomized to esmolol and propranolol except that the diastolic blood pressure was 5 mm Hg higher among the esmolol efficacy patients (Table I). There was no significant interaction between the treatment assignment and study centers.

Efficacy: During titration, 72% (36 of 50) of patients had a therapeutic response to esmolol compared with 69% (38 of 55) of patients randomized to propranolol (NS). During the 4-hour maintenance period, 67% (20 of 30) on esmolol and 58% (21 of 36) on propranolol maintained therapeutic response. Table II details the specific types of therapeutic response during each of these 2 periods. The therapeutic response rate within each treatment group did not differ with regard to those patients younger than or over 65 years of age, gender, postoperative status or type of heart disease. There was also no difference in response rates among types of SVT between esmolol and propranolol. Therapeutic response in patients with atrial fibrillation was similar in both treatment groups: esmolol, 28 of 38 (74%) and propranolol, 34 of 46 (74%). Figure 1 details the cumulative and relative therapeutic response rates among efficacy patients randomized to esmolol during the titration period. In the esmolol group 70% (35 of 50) of patients responded to an infusion rate of ≤200 μg/kg/min. One additional patient responded at 250 μg/kg/min, while no additional patients responded to the 300 μg/kg/min dose. The average dose of esmolol in responders was 115 ± 11 μg/kg/min. Figure 2 illustrates the cumulative and relative therapeutic response rates among propranolol efficacy patients. Cumulative therapeutic response at 3 mg of propranolol was 31% (17 of 55) and at 6 mg of propranolol or less, it was 69% (38 of 55).

Response to propranolol or esmolol could not be predicted by any of the demographic characteristics except that in the propranolol treatment group, nonresponders had a higher mean HR (155 beats/min) than the responders (141 beats/min). Baseline systolic blood pressure was slightly higher among responders than nonresponders within each of the treatment groups. Concurrent digoxin therapy was also associated with a higher therapeutic response in both treatment groups. For example, 85% (22 of 26) of patients in the esmolol group who were receiving digoxin were therapeutic responders compared with 58% (14 of 24) of patients not taking digoxin who were therapeutic responders. Similarly, 75% (21 of 28) of patients in the propranolol group on digoxin were therapeutic responders compared with 63% (17 of 27) of those without concurrent digoxin were therapeutic responders.

As shown in Figure 3, during the follow-up period, the HR more rapidly reversed itself among the esmolol

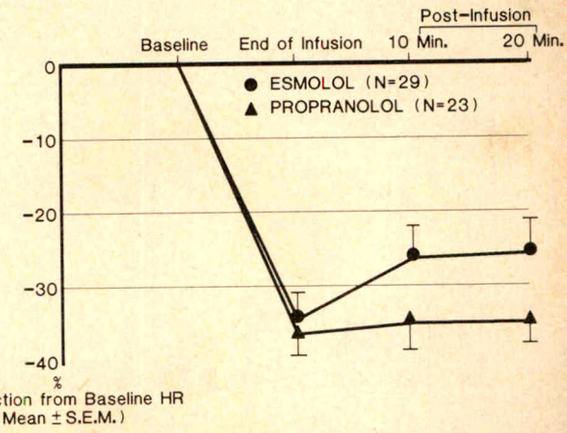

FIGURE 3. Recovery of heart rate during the follow-up period (after discontinuation of study drugs) in efficacy patients who were therapeutic responders. In esmolol-treated patients, study drug was discontinued after 4-hour maintenance period. In propranolol-treated patients, study drug was discontinued after 10 minutes in the titration period (4 hours, 10 minutes after boluses). These patients were infused with placebo esmolol throughout the 4-hour maintenance period.

TABLE III Adverse Reactions Noted During the Study

Adverse Reaction	No. of Patients*	
	Esmolol	Propranolol
Hypotension	23	4
Asymptomatic	19	3
Symptomatic	4	1
Ventricular ectopy	1	0
Excessive bradycardia	0	2
Congestive heart failure	0	1
Diaphoresis	4	0
Dyspnea, rales, cyanosis	2	2
Dizzy, weakness, headaches	2	1
Nausea, vomiting, dyspnea	0	6
Intravenous site irritations	5	0

* A patient may have more than 1 adverse reaction.

patients (within 10 minutes after discontinuation of esmolol) compared with those on active propranolol (approximately 4 hours after discontinuation of active propranolol).

Safety results: A total of 29 (45%) esmolol patients and 11 (18%) propranolol patients developed adverse reactions during the study (Table III). The most frequently reported adverse reaction was hypotension, which was symptomatic in 4 patients receiving esmolol and 1 receiving propranolol. These 4 patients received doses ≥150 μg/kg/min and hypotension resolved within 20 to 90 minutes after discontinuation of esmolol. Most patients in whom hypotension developed in the esmolol group were postoperative, had atrial fibrillation or were over 65 years of age. Premature discontinuation from the study because of adverse reactions occurred in 15 patients receiving esmolol and in 6 receiving propranolol. All esmolol patients were discontinued due to hypotension. Adverse reactions, which necessitated discontinuation among 6 propranolol patients, were: increasing heart failure (n = 1), dyspnea and cyanosis (n = 1), bradycardia and hypotension (n = 1), nausea (n = 1), nausea and hypotension (n = 1) and nausea, vomiting and headache (n = 1). One patient died in each treatment group because of development of ventricular fibrillation within 24 hours of discontinuing the β blocker and in neither case was death considered to be related to the study drug administration. The incidence of adverse reactions was higher in esmolol patients receiving ≥ 200 μg/kg/min (21 events) compared with those receiving less than this dose (13 events). Of the 17 adverse events in the propranolol group, 9 occurred in patients receiving <3 mg and 8 in those who received between the 3- to 6-mg dose. No significant differences were noted among any of the laboratory variables in patients in this study.

Discussion

Beta-blocker therapy has proved to be particularly effective in treating patients in the intensive care unit with unstable ischemic, hypertensive and arrhythmic disorders.[1] Intravenous use of metoprolol has recently been shown to be effective in decreasing the prevalence of serious ventricular arrhythmias and mortality from acute myocardial infarction.[4] The elimination half-life of β blockers, however, when used in this setting typically ranges from 2 to 6 hours.[2] Because β blockers may cause a deterioration or worsening of left ventricular dysfunction, excessive bradycardia, advanced degrees of conduction disturbances and bronchospasm, the potential use of an ultrashort-acting β blocker, particularly in the intensive care unit, would provide enhanced safety in these high-risk patients. Esmolol was recently developed and shown in animal and human studies to be a cardioselective β blocker with no intrinsic sympathomimetic activity.[5–8] The electrophysiologic data of esmolol demonstrate its rapid onset and offset of β-blocker effects on the sinus and atrioventricular node.[9]

This multicenter study demonstrated that esmolol, when infused in the dosage range of 50 to 300 μg/kg/min, was as effective as propranolol given from 3 to 6 mg over a 30-minute titration period to patients with SVT by producing a reduction in HR or conver-

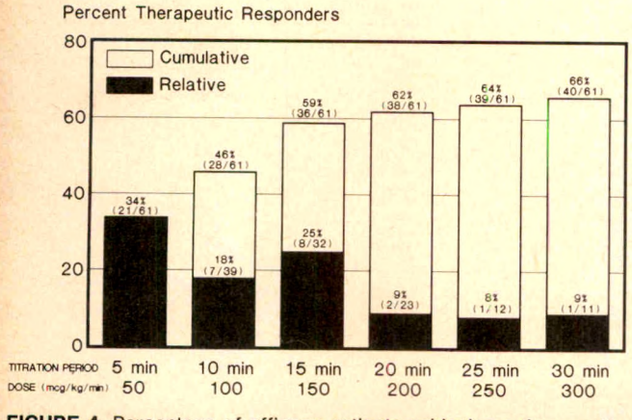

FIGURE 4. Percentage of efficacy patients achieving a therapeutic response during the initial and crossover esmolol titration periods, by esmolol dosage, in a multicenter, placebo-controlled, double-blind study. Cumulative percent is the number of responders at a given dosage or lower, divided by the number of efficacy patients (n = 61). Relative percent is the number of responders at a given dosage divided by the number of efficacy patients treated with that dosage.

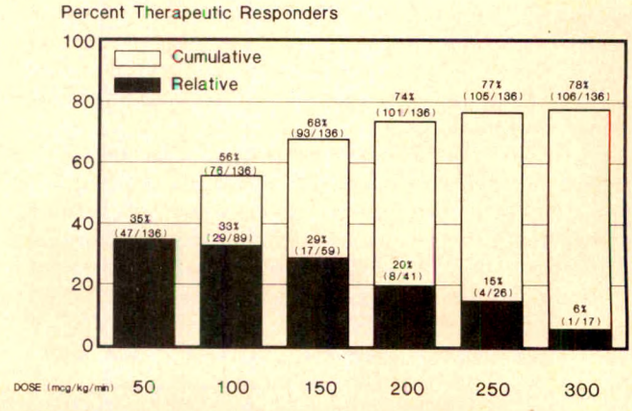

FIGURE 5. Percentage of efficacy patients achieving a therapeutic response during the titration period, by esmolol dosage, in an open-label, multicenter study. Cumulative percent is the number of responders at a given dosage or lower, divided by the number of efficacy patients (n = 136). Relative percent is the number of responders at a given dosage divided by the number of efficacy patients treated with that dosage.

TABLE IV Adverse Reactions Observed Among SVT Patients Treated with Esmolol (Infusion up to 24 Hours)

Body System/Adverse Reaction	(n)*	%†
Cardiovascular		
Hypotension	70	44
Symptomatic	(21)	(13)
Asymptomatic	(49)	(31)
Diaphoresis	16	10
Other	19	12
Total‡	81	51
Central nervous system		
Somnolence	11	7
Agitation	7	4
Headache	6	4
Dizziness	6	4
Confusion	5	3
Other	12	8
Total‡	39	24
Gastrointestinal		
Nausea	20	13
Other	10	6
Total‡	26	16
Respiratory		
Dyspnea, bronchospasm rhonchi or wheezing	4	3
Other	4	3
Total‡	8	5
Skin		
Inflammation (IV site)	8	5
Induration (IV site)	7	4
Infiltration (IV site)	7	3
Other	5	3
Total‡	24	15

* Number of patients reported to have the respective adverse reaction.

† Total number of patients treated with esmolol = 160.

‡ Frequently, a single patient was reported to have more than 1 adverse reaction.

sion to normal sinus rhythm. In addition, esmolol exhibited a more rapid attenuation of its negative chronotropic effect after its termination compared with propranolol, which is a finding consistent with its ultrashort-acting pharmacokinetics. Therapeutic response in the 2 treatment groups was not influenced by differences in age (<65 vs ≥65 years), gender, type of SVT, primary diagnosis and postoperative status.

Although more esmolol patients developed asymptomatic hypotension (systolic blood pressure <90 mm Hg) than patients on propranolol, this hypotension largely caused no symptoms and no lasting adverse consequences. Hypotension occurred more frequently in the elderly and postoperative patient group with atrial fibrillation. In most patients (16 of 23), hypotension resolved within 30 minutes after discontinuation of esmolol. The fact that most patients responded to 50 to 150 μg/kg/min but were then advanced to higher doses (>200 μg/kg/min), which resulted in hypotension, suggests that hypotension might be avoided with more careful esmolol titration.

In a multicenter, double-blind, randomized, partial crossover study, esmolol (64%) was found to be more effective than placebo (8%) in the treatment of patients with SVT (Fig. 4).[10] In this study, most responders achieved response at doses of 50 to 150 μg/kg/min of esmolol. Further, it has been shown that in these patients, after discontinuation of esmolol, HR returned to preinfusion level within 30 minutes. This indicates that esmolol as used in the present study is similar to findings observed in a placebo-controlled study. In a multicenter, open-label study, esmolol infused for durations up to 24 hours was found to be effective and well tolerated in patients with SVT (Fig. 5).[11] The average dose of esmolol among responders was 97.2 ± 5.5 μg/kg/min. In most responders (90%), therapeutic response was sustained during the maintenance period and the response rate was similar among patients with atrial fibrillation, atrial flutter, sinus tachycardia and other types of SVT. Although the incidence of hypotension (symptomatic, 13% and asymptomatic, 31%) was more frequent than other adverse reactions among patients infused for durations of up to 24 hours (Table IV), in most of these patients (92%) hypotension resolved either during esmolol infusion or 30 minutes after discontinuation of esmolol. Thus these results are similar to the findings of the present study.

Esmolol has other potential applications that have been studied to date, including its effect on decreasing ischemic necrosis as shown by a reperfusion myocardial infarction study in dogs.[12] Its use in anesthesia to decrease HR acceleration and to control postoperative tachycardia has also been reported.[13,14] Its potential role in the treatment of acute hypertensive emergencies and in the management of ventricular arrhythmias is yet to be fully explored. These data suggest that esmolol deserves further trial in patients with unstable cardiovascular states, particularly because of its potency and the fast elimination of the β-blocking effects when its infusion is discontinued.

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Discussion

Dr. Iskandrian (Philadelphia, Pennsylvania): Dr. Morganroth, hypotension in the postoperative patient is always a problem by itself. These patients have several IV lines running and their fluid balance is generally not good. I would like to know: Was there anything unusual about these patients who had hypotension? Were they postoperative patients? Was their left ventricular function compromised? Was an attempt made to titrate the dose down and continue the infusion at the lower rate? Was the hypotension observed without an effect on the rate, or was it a concomitant effect with the rate changes?

Dr. Morganroth (Philadelphia, Pennsylvania): One of the deficits of doing a controlled study, particularly a double-blind study involving many centers, is that one doesn't have the flexibility of acting in an open fashion. So the answers to most of your questions are no, because we didn't have the luxury of being able to have the patients' doses of esmolol titrated down or up, depending on a clinical response. It was all rigidly controlled by protocol by a study nurse in order to justify the pooling of multicenter data. I do not have any information regarding the data in this study relative to what percentage of the patients with asymptomatic hyotension would have had just as good an efficacy endpoint at, say, a 50 μg/kg/min decrease of their infusion, which is what you suggest. I have no doubt that would occur, which is suggested from just looking at the distribution of patients in the various groups where adverse effects occur. In terms of whether there was anything special about that group—were they closer to being right out of the operating room or were there any other factors that could be identified—the answer is no. Unfortunately, we do not have very precise measurements. For example, ejection fraction data per se on these patients are not available, so we could not identify any specific factor.

Dr. Gray (Los Angeles, California): I might be able to provide a partial answer to your question. We participated in an open-label supraventricular tachyarrhythmia study, in which all our patients were postoperative. The results were published in the June 1985 Journal of the American College of Cardiology. There were 24 patients and we used a similar protocol, except that it was an open-label, 1-drug study with no comparison. We had virtually the same incidence of hypotension as an adverse effect in which the substrate was the same—atrial fibrillation and some sinus tachycardia. Of our 12 patients who experienced hypotension, all but 2 could be continued on the drug by lowering the dose. In other words, we could wean back the dosage, maintain heart rate control to a reasonable extent and avoid the hypotension. In 2 patients we did have to discontinue the drug because of hypotension. In this particular study population, on average, the ejection fraction was in the low-normal range. There were patients who were in the decidedly abnormal range and some were in the clearly normal range. So, like all the other clinical work here, it is a mixture of things. My impression is that in patients who are fluid-depleted, or who have potential for subclinical fluid depletion, that is a factor related to hypotension. For instance, giving concomitant intravenous fluid challenge will sometimes raise the blood pressure and allow you to continue the dose of esmolol at the same level. But, by and large, we would first titrate back the dose of esmolol.

Dr. Morganroth: I think what we have learned this morning from the clinical pharmacology data was that peripheral vascular resistance does not increase on esmolol; therefore, esmolol is not a vasodilator. At least esmolol does not increase peripheral resistance; therefore, volume is going to be an important issue in these patients versus propranolol, in which one would expect some peripheral resistance to help compensate for a lowering of blood pressure. With esmolol, one won't have that compensation, and a fluid challenge may be the best first treatment, perhaps with some simultaneous decrease in the esmolol dose.

Dr. Kirshenbaum (Boston, Massachusetts): Thirty percent of the patients had coronary artery disease, at least as a label, presumably because they had a history of angina or a history of prior infarctions. Were any of them actively ischemic at the time they received the drug and had the tachycardia?

Dr. Morganroth: No, that would be an exclusion criterion for a protocol such as this, because one would want to treat active ischemia, particularly in an intensive care unit. I can only speak for my own patients, but it presumably holds for all the other investigators that none of the patients would have had either any obvious ischemia by any criteria, or, in fact, anything that would require immediate treatment, such as ventricular arrhythmias—nonsustained ventricular tachycardia, for example.

Dr. Kirshenbaum: In your off-drug heart rate response, at 20 minutes the esmolol population was still roughly 20% below their baseline heart rate. Is this because some of them had converted to a sinus rhythm and, therefore, would not return to the tachycardia? Or was it that, if you had waited 40 minutes or an hour, you would have seen them return to their baseline tachyarrhythmia?

Dr. Morganroth: I think there are multifactorial reasons why the esmolol patients' heart rates were still not back to baseline, after a few half-lives had passed. The reason is that after their acute arrhythmia is identified and IV lines are begun, they are asked to sign a consent form and they are watched by several people. I would postulate that their catecholamine levels are relatively high because they are frightened. After 1 or 2 hours—or actually up to 4 hours in most patients—they settle down and, therefore, their heart rate is as if they had been on placebo the entire time. If we had a placebo group, I would suspect that the esmolol group at 20 minutes would be identical to a placebo group.

Dr. Reves (Durham, North Carolina): Was there any difference in the degree of hypotension among centers? This gets at the point again about sympathetic tone; postoperatively, I know there is a lot of differene in the emergence from various anesthetic regimens that, I doubt, were controlled in this.

Dr. Morganroth: No, anesthetic regimens were not controlled among the centers.

Dr. Lee (McGaw Park, Illinois): A point of clarification: You mentioned you had 4 patients with symptomatic hypotension that had to be discontinued from study. You also mentioned 15 patients that were prematurely terminated because of hypotension. Could you clarify this?

Dr. Morganroth: Those 15 included the 4 who were terminated early because of symptomatic hypotension. They also included many of the patients who were terminated because of reaching a blood pressure of 90 mm Hg, and the physician said, well, that's good enough, let's stop the patient at this point. Obviously, in the clinical setting there would be no reason not to have continued many of these patients on esmolol and, whether given fluid or not, they would have done perfectly well. So, premature discontinuation of esmolol does not necessarily mean it was done for medically necessary reasons. It was more for study protocol reasons.

Dr. Lee: As you know, we are doing a study now comparing esmolol with verapamil in supraventricular tachyarrhythmia, and this is a hypothetical question because I don't know the answer yet as to how the study is going. But, if we assume that esmolol was as effective as verapamil in this study in terms of lowering ventricular rate, would you view esmolol as a possible agent to use before verapamil because of its short half-life? Would you use esmolol first, for example, and then if it didn't work, use verapamil?

Dr. Morganroth: This is a very good question. I think it was addressed a little bit by Allan Greenspan this morning. The question is, if as a physician I have a patient with supraventricular tachycardia and I have 2 drugs I could reach for on the shelf, one being esmolol and one being verapamil, which would I choose first? I think in this kind of population, I would have no hesitancy to argue that esmolol should be reached for first, for a very simple reason. I suspect verapamil is more potent compared with esmolol in terms of suppressing atrioventricular nodal conduction. Therefore, if I have a patient and I am not quite sure of how the left ventricle is going to react to the 2 drugs, I would much rather pick a drug with a very short half-life, such as esmolol, rather than verapamil, which has a much longer half-life. Then, if esmolol doesn't work, I would probably have no reason to hesitate using a smaller dose of verapamil to add to esmolol. The combination of these 2 drugs in the refractory patient—which should be uncommon—might be very useful, but the dose of verapamil would have to be kept very small.

Experimental and Clinical Observations on the Efficacy of Esmolol in Myocardial Ischemia

ROBERT A. KLONER, MD, PhD, JAMES KIRSHENBAUM, MD, RUDIGER LANGE, MD, ELLIOTT M. ANTMAN, MD, and EUGENE BRAUNWALD, MD

Beta blockers reduce myocardial oxygen demand and are therefore useful in ischemic states. They reduce angina pectoris and reduce the risk of death when administered long-term after acute myocardial infarction. Some studies suggest that when administered early after coronary occlusion they can reduce myocardial infarct size. Relative contraindications to β blockers, such as a history of congestive heart failure, chronic obstructive lung disease, atrioventricular conduction defects and low blood pressure, limit their use. Conventional β blockers have a relatively long duration of action and are either contraindicated or must be used with particular caution in patients with these contraindications. Esmolol is an ultrashort-acting β blocker with a biologic half-life of 9 minutes. Therefore, such an agent may be useful in patients with ischemic heart disease in whom reducing heart rate would be beneficial but in whom there is concern that β blockers might not be tolerated. Esmolol reduced myocardial infarct size in 2 experimental studies of coronary occlusion followed by reperfusion, and improved the recovery of the stunned myocardium when administered during experimental myocardial ischemia. Esmolol's brief duration of action may make it safer than conventional β blockers for the management of patients with unstable angina or myocardial infarction.

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Experimental and clinical studies confirm that β-adrenergic blockers have beneficial effects during myocardial ischemia.[1] Beta blockers are useful in treating angina pectoris[2–4] and have been shown to reduce mortality when administered long-term to patients who have recovered from myocardial infarction.[5–7] Whether the acute administration of β blockers is capable of reducing myocardial infarct size remains controversial. Some experimental and clinical studies have shown that β blockers do reduce myocardial infarct size,[8] while others have failed to show this effect.[1,9] Nevertheless, β blockade remains an important means by which to reduce myocardial oxygen demand and thereby diminish ischemia in the setting of unstable angina, chronic stable angina and angina pectoris occurring after myocardial infarction. However, because β blockers have the potential for exacerbating congestive heart failure, for impairing conduction, for reducing blood pressure and for precipitating bronchospasm, they are not used in some patients, especially during the periinfarction period.

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In recent studies, 18 to 28% of postinfarct patients could not receive β blockade because of the presence of absolute or relative contraindications.[5–7] The potential advantage of an ultrashort-acting β-blocking agent is that it can be administered to patients who could potentially benefit from a reduction in myocardial oxygen demand, but who may not be able to tolerate β blockade. The short biologic half-life (9 minutes) of esmolol allows this drug to be administered to such patients, with the knowledge that if they cannot tolerate β blockade, the effects of the drug are rapidly reversed by simply discontinuing the infusion.[10]

Experimental Studies of Conventional Beta Blockade in Ischemic Heart Disease

There is substantial experimental evidence that β blockers protect ischemic myocardium.[1] The ability of these agents to reduce actual ischemic cell death, however, remains controversial. Dog studies showed that propranolol and practolol reduced epicardial and precordial ST-segment elevation consequent to occlusion of the left anterior descending coronary artery.[11–14] Hillis et al[15] showed that pretreatment with propranolol significantly blunted the rise in intramyocardial P_{CO_2} (a measure of myocardial ischemia[16]) after coronary occlusion, suggesting that β blockade reduced the severity of ischemia. Goodlet et al[17] demonstrated that

propranolol infused directly into an ischemic area of myocardium preserves high-energy phosphate levels. In addition, propranolol has been shown to reduce the ultrastructural changes that occur during the first few hours of coronary occlusion, including the extent of mitochondrial swelling,[18] and extent of microvascular injury.[19] Possible mechanisms of action are shown in Table I.

Studies that have assessed the ability of β blockers to reduce the extent of ischemic cell death after coronary artery occlusion have shown mixed results. Maroko et al[12] showed that for similar degrees of epicardial ST-segment elevation 15 minutes after occlusion but before treatment, animals receiving propranolol had less depletion of creatine kinase activity at 24 hours. In other experimental studies, propranolol was shown to reduce the extent of necrosis estimated from loss of electrocardiographic R waves and development of Q waves,[20] and in others to reduce infarct size as assessed by pathology.[21] Miura et al[22] suggested that the ability of a β blocker to reduce infarct size was highly dependent on the time at which the agent was administered in relation to coronary occlusion. Thus, while pretreatment with β blockade reduced infarct size by 53%, when β blockade was administered 3 hours after occlusion, the reduction of infarct size was 28%, and when administered 6 hours after coronary occlusion, no effects were observed.[22]

However, there have been a number of studies in which β blockade was shown to have *no* beneficial effect on myocardial infarct size. For example, Cheng et al[23] showed that pretreatment with propranolol had no effect on infarct size in primates with 2 hours of coronary occlusion and reperfusion, while Reimer and Jennings observed that propranolol failed to reduce the extent of necrosis in dogs when the coronary occlusion was maintained for 3 hours followed by reperfusion.[24] Peter et al[25] also showed no benefit of propranolol on experimentally produced infarcts. Lange et al[26] showed that metoprolol and pindolol failed to reduce infarct size in a permanent coronary artery occlusion model in which the "area at risk" of developing necrosis was measured with radioactive microspheres. Reynolds et al[27] also showed that β blockade was ineffective in reducing the size of experimentally induced myocardial infarcts in the dog with permanent coronary artery occlusion, but was effective in reducing infarct size when 1 hour of coronary occlusion was followed by reperfusion.

The reason for the discrepancies in the results among the various studies showing a beneficial effect versus those showing no effect of β blockers on infarct size remains to be elucidated. One possibility is that β blockers, by reducing the myocardial oxygen demand, only *delay* the death of ischemic cells. If reperfusion is carried out early enough, at a time when treated cells are still viable (because the drugs have delayed cell death), then β blockers may reduce infarct size. If on the other hand, reperfusion is not instituted at all or is initiated too late, then eventually all cells destined to undergo ischemic cell death do so, and β blockers fail to reduce infarct size.

TABLE I Possible Mechanisms of Action by Which Beta Blockers Reduce Ischemic Injury

*	Reduction of myocardial oxygen consumption by blockade of β-adrenergic receptors (decreased heart rate and contractility)
	Decreased lipolysis and myocardial free fatty acid uptake shifting utilization of myocardial substrate to glucose
	Redistribution of coronary collateral flow toward the more ischemic subendocardium
†	Shifting the O_2-hemoglobin dissociation curve to the right
†	Direct membrane-stabilizing effect
†	Alteration of platelet function

* Principal mechanism of action.
† Mechanism of little or no importance.

Experimental Observations on the Effects of Esmolol

Effect of esmolol on experimental myocardial infarct size: Lange[28] studied the ultrashort-acting β blocker esmolol in dogs subjected to a 3-hour experimental occlusion of the left anterior descending artery followed by 3 hours of coronary reperfusion. Treated dogs received a continuous infusion of esmolol, begun 15 minutes after coronary occlusion, with the dose titrated to reduce heart rate by 20% (100 to 150 μg/kg/min). The "area at risk" determined in vivo was similar in both groups. In control animals, 73 ± 6% of the ischemic area at risk became necrotic, while in treated animals only 48 ± 7% became necrotic ($p < 0.025$). While untreated animals showed a deterioration in cardiac function in the early phases of reperfusion, no such deterioration of function occurred in the esmolol-treated group. Lange's investigation confirmed and extended a study by Zaroslinski et al,[10] which showed that esmolol reduced infarct size when coronary occlusion was maintained for 1 hour followed by 1 day of coronary reperfusion.

Therefore, in a coronary reperfusion model, esmolol reduced myocardial infarct size and prevented early functional deterioration after coronary artery reperfusion.

Effect of esmolol on stunned myocardium in experimentally induced myocardial ischemia: Recent experimental studies have shown that brief periods of transient coronary occlusion followed by reperfusion, in which no necrosis develops, can result in relatively prolonged depression of regional function, cardiac ultrastructure and high-energy phosphate levels. This phenomenon has been referred to as stunning of the myocardium.[29] It occurs not only in experimental models of acute ischemia,[30–32] but may also occur in patients with unstable angina[33] and in those with multivessel coronary artery disease who develop exercise-induced angina.[34] Postischemic depression of ventricular function, i.e., myocardial stunning, may also occur in some patients who receive thrombolytic therapy for acute myocardial infarction in whom there is little or no immediate return of cardiac function following reperfusion, but in whom function is improved 10 to 14 days after reperfusion.[35]

Three of the coauthors carried out an investigation (presented in part at the annual meeting of the American College of Cardiology, 1983[36]) designed to determine whether esmolol enhances functional recovery when given before and during brief coronary occlu-

sion. Sodium pentobarbital-anesthetized open-chest dogs were intubated and mechanically ventilated. Heart rate and arterial pressure were recorded and the left ventricle was instrumented with ultrasonic crystals in order to measure the percent systolic shortening of regional myocardial segments. The proximal left anterior descending coronary artery was occluded with a Schwartz atraumatic vascular clamp for 15 minutes, followed by 4 hours of reperfusion induced by abruptly removing the clamp. This period of ischemia has been shown to be too brief to induce tissue necrosis, but does mimic severe coronary spasm in man. Twelve dogs received esmolol (100 to 150 μg/kg/min) commencing 1 hour before the occlusion and ending at the onset of reperfusion, while 12 control dogs received saline. Regional myocardial blood flow was measured 10 minutes after coronary occlusion.

With coronary occlusion, there was an increase in left ventricular (LV) end-diastolic pressure in both groups (Fig. 1). With esmolol infusion, heart rate fell from 147 to 122 beats/min ($p < 0.001$) and remained significantly lower than in the control dogs during the coronary occlusion. Following reperfusion, heart rate in control and treated groups was similar, confirming that β blockade is rapidly terminated after esmolol infusion is discontinued.

LV end-diastolic pressure tended to be lower during the reperfusion phase in the dogs that had received esmolol, although this difference was not significant.

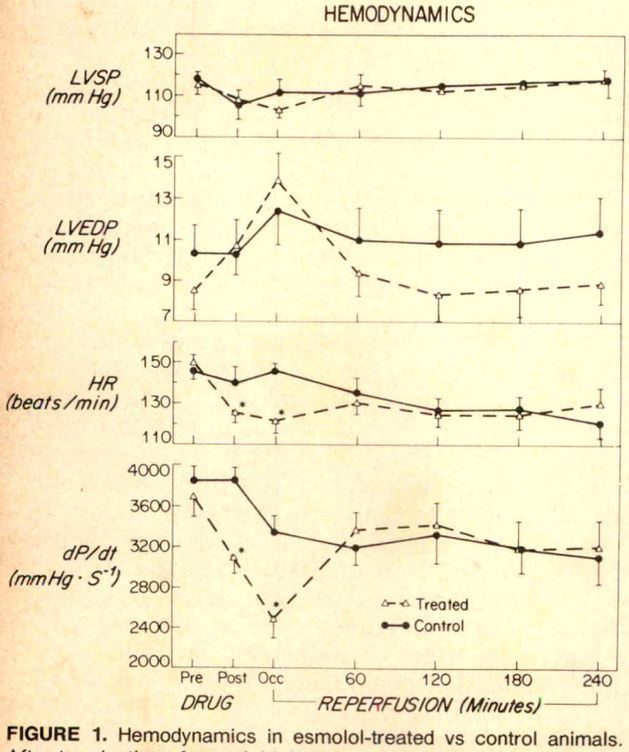

FIGURE 1. Hemodynamics in esmolol-treated vs control animals. After termination of esmolol infusion at reperfusion, heart rate (HR) and dP/dt come back to baseline during the remainder of the experiment. LVSP = left ventricular systolic pressure; LVEDP = LV end-diastolic pressure; dP/dt = change in pressure over change in time. Pre = pre-drug therapy; Post = post-drug; OCC = occlusion.

There was a significant fall in dP/dt during the infusion of esmolol and the fall in dP/dt during coronary occlusion was greater in the treated than in the control group (Fig. 1). Upon coronary reperfusion and termination of esmolol infusion, dP/dt in the control and treated groups was similar, confirming esmolol's short half-life.

Typical waveforms of subendocardial segmental wall motion from a control animal and an esmolol-treated animal are shown in Figure 2. In both groups, preocclusion waveform morphology showed active contraction (segment shortening) as demonstrated by a reduction in the distance between crystals during systole (downward deflection on the tracing). After 15 minutes of coronary occlusion the ischemic myocardial segments bulged paradoxically during systole. After 4 hours of reperfusion, systolic bulging was less intense, but was still present in the control dog. In contrast, the dog that had been treated with esmolol during occlusion showed active contraction during the reperfusion phase.

The extent of systolic shortening of the subendocardium in control and esmolol-treated animals is compared in Figure 3. Before coronary occlusion, systolic shortening was positive, reflecting active contraction. During coronary occlusion, systolic shortening became negative; i.e., paradoxical bulging occurred. Upon reperfusion, there was some recovery in both groups; but after 4 hours of reperfusion in controls there was, on the average, still no active contraction, indicating severe stunning of the myocardium. In contrast, systolic shortening did occur in animals that had received esmolol. In control animals, recovery of subendocardial wall motion was only 8% of preocclusion value, while in esmolol-treated animals recovery was 48% ($p < 0.05$). Although improved recovery was observed with esmolol in the subendocardium, the degree of recovery in the subepicardial tissue did not differ between groups.

There was a trend, which was not statistically significant, for regional myocardial blood flow to be lower in the esmolol-treated group in both ischemic and nonischemic subepicardium and subendocardium (Fig. 4). These findings suggest that the beneficial hemody-

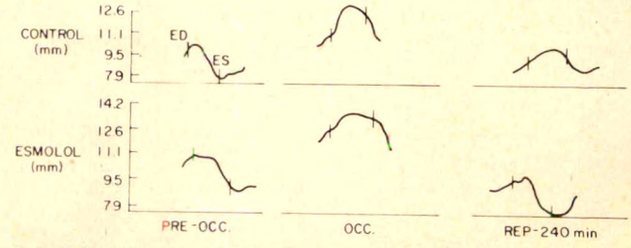

FIGURE 2. Waveform tracings show segment length between a pair of ultrasonic crystals within the ischemic zone of a control vs esmolol-treated animal. Vertical markings represent end-diastole (ED) and end-systole (ES). Preocclusion (PRE-OCC.), the left ventricular segment shortens during systole in both animals; during coronary occlusion (OCC.) there is paradoxical systolic bulging in both animals. With reperfusion (REP) there is active shortening in the esmolol-treated animal; paradoxical bulging persists in the control animal (stunned myocardium).

namic effects of esmolol during the reperfusion phase were not due to greater blood flow during coronary occlusion.

Thus, in the anesthetized open-chest dog with transient myocardial ischemia, esmolol reduced heart rate significantly, an action that was rapidly reversed upon termination of esmolol infusion. Esmolol also accelerated postischemic recovery of reperfused, stunned subendocardium.

Clinical Studies of Beta Blockers in Ischemic Heart Disease

Beta blockers are now widely used for the treatment of angina pectoris, and several studies have shown that they reduce the frequency of angina and increase the threshold for the development of angina.[2–4] In addition, β blockade increases the threshold for developing angina pectoris, even in those patients whose heart rate is maintained constant by atrial pacing.[37]

When administered to patients with acute myocardial infarction, β blockers have been shown to reduce heart rate, arterial pressure and cardiac output with small and variable changes in LV filling pressures;[38–40] in addition they narrow the arterial-coronary sinus oxygen difference and lessen myocardial lactate production.[38] Mueller et al[40] showed that in patients without contraindications to β blockade, propranolol reduces myocardial oxygen consumption and does not cause large increases in pulmonary capillary wedge pressure. Propranolol reduces plasma catecholamine concentrations during evolution of infarction and shifts the metabolism from that of free fatty acids to carbohydrates.[38,41]

Several clinical studies have shown that β blockade is capable of reducing ST-segment elevation during myocardial infarction;[39,42,43] in addition, Waagstein and Hjalmarson demonstrated that these agents reduce ischemic chest pain during infarction.[44]

Clinical studies that have assessed the ability of β blockers to reduce myocardial infarct size have provided mixed results, not dissimilar to experimental results. Yusef et al[45] reported that intravenous atenolol administered during the early phase of infarction reduced MB-CK release. Early administration of metoprolol, alprenolol or timolol has been shown to reduce infarct size, estimated by enzymatic techniques or QRS analysis.[8,46–48] Peter et al[49] reported that patients treated with propranolol within 4 hours of onset of symptoms had lower peak CK values and less cumulative CK appearance. Norris et al[50] showed that propranolol reduced the incidence of threatened myocardial infarction.

On the other hand, there have been several studies in which β blockers had no effect on myocardial infarct size in humans. A large multicenter study to assess the effect of propranolol on infarct size, measured by both enzymatic technique and electrocardiographic QRS mapping, showed no beneficial effect;[9] however, in this study, patients did not receive the β blocker until an average of more than 8 hours after symptoms—a time at which it may have been too late for propranolol to have either delayed cell death or salvaged tissue. Johansonn[51] studied the effects of 1 dose of intravenous practolol followed by oral atenolol in patients with acute myocardial infarction and found no difference in peak CK elevations or ST elevations.

There is less dispute about the efficacy of β blockers in the post–myocardial infarction patient. There have been several recent well-controlled clinical trials that have shown that when β blockers are administered chronically after acute myocardial infarction, long-term mortality is reduced.[5–7] Results from 3 of these

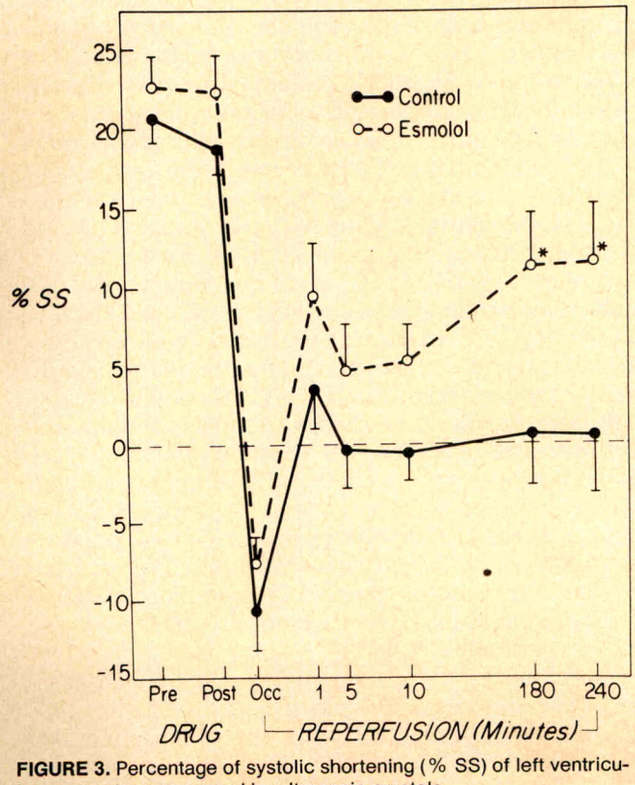

FIGURE 3. Percentage of systolic shortening (% SS) of left ventricular segments as assessed by ultrasonic crystals.

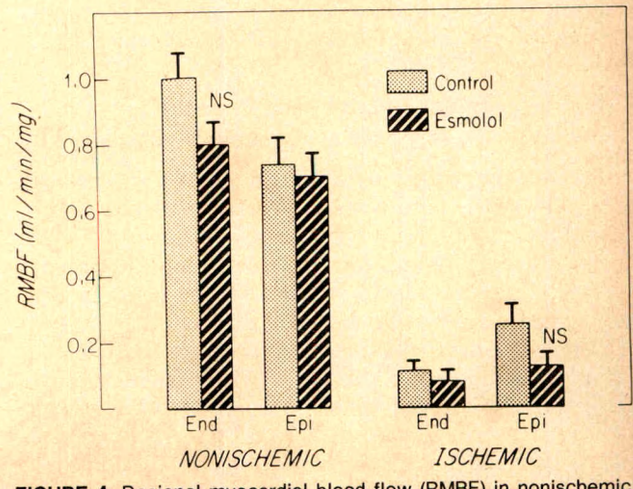

FIGURE 4. Regional myocardial blood flow (RMBF) in nonischemic and ischemic myocardium in control and esmolol-treated animals.

TABLE II Recent Controlled Trials of Beta Blockade After Acute Myocardial Infarction (AMI)[2]

Study	Country	Beta Blocker Studied	No. of Pts	Time Treatment Instituted	Dose (mg/day)	Effect on Mortality	Follow-up Time (months)
Norwegian Multicenter study Group, 1979[5]	Norway	Timolol (vs placebo)	1,884	1–4 weeks after AMI	20	Sudden deaths: Timolol: 47† (n = 945) Placebo: 95 (n = 939) Other cardiac deaths: Timolol: 11* Placebo: 18	12–36
Hjalmarson et al, 1981[6]	Sweden	Metoprolol (vs placebo)	1,395	Immediately after AMI	15 IV, then 200	Mortality: Metoprolol: 40* (n = 698) Placebo: 62 (n = 697)	3
Beta-Blocker Heart Attack Trial Research Group, 1982[7]	U.S.	Propranolol (vs placebo)	3,837	1–3 weeks after AMI	180–240	Sudden deaths: Propranolol: 64* (n = 1,916) Placebo: 89 (n = 1,912) Total mortality: Propranolol: 138‡ Placebo: 188	36

*$p < 0.05$; †$p < 0.001$; ‡$p < 0.005$.
Reprinted with permission from Hjalmarson.[54]

studies are summarized in Table II. The mechanism of action by which β blockers reduce long-term mortality is under investigation. In the Beta-Blocker Heart Attack Trial,[7] propranolol was begun 5 to 21 days after infarction. Hence, reduced mortality in this study could not have been related to any beneficial effect on myocardial infarct size. It appears that β blockers may reduce incidence of ventricular arrhythmias in the chronic phase of infarction;[52] they reduce the incidence of sudden death and of reinfarction, and it is also possible that they protect the myocardium against further episodes of ischemia or infarction. The results of these clinical studies are clear enough to warrant treatment with β blockers of patients who have suffered acute myocardial infarction and who have no contraindications to this type of therapy.

In summary, β blockers are useful for the treatment of angina pectoris and appear to exert beneficial effects in patients with acute myocardial infarction—including reduced oxygen demand, reduced mortality and, in some studies, reduced infarct size as well.

Effect of Esmolol in Patients with Acute Myocardial Ischemic Syndromes

The relatively long durations of actions of currently available β blockers raise concern about the use of these agents in certain subgroups of patients with acute ischemia or infarction. These include patients with LV dysfunction in whom there is concern that severe heart failure may be precipitated; patients with slightly prolonged PR intervals in whom there is concern of precipitating further atrioventricular block; patients with a history of smoking or chronic obstructive lung disease in whom there is concern of precipitating bronchospasm; and patients whose blood pressure is on the low side of normal in whom there is concern of precipitating hypotension. The risk of developing these complications may limit the use of β blockers in the very patients in whom reduction of oxygen demand would be most useful. Because the duration of action of esmolol is only minutes, patients may receive this drug with relative safety; if adverse effects develop, the drug can simply be stopped and the adverse effects rapidly reversed. This is not the case with conventional β blockers, which require several hours to dissipate. Kirshenbaum et al[53] recently reported the results of a study in which the safety and efficacy of esmolol in lowering the ventricular rate was determined in patients with myocardial ischemia. The study group consisted of 5 patients with acute myocardial infarction, 10 patients with post–myocardial infarct angina and 4 patients with unstable angina, all of whom had a heart rate >60 beats/min. After baseline hemodynamic measurements, esmolol was administered in maximum doses of 300 μg/kg/min and infused for up to 420 min. Heart rate fell from 92 ± 11 (mean ± standard deviation) to 77 ± 13 beats/min ($p < 0.01$), and systolic arterial pressure fell from 120 ± 13 to 97 ± 11 mm Hg ($p < 0.01$) during the initial 30-minute infusion period, and these parameters remained significantly reduced throughout the infusion. Thirty minutes after terminating the infusion of esmolol, heart rate returned to within 4% of baseline values and mean arterial pressure to within 6% of baseline values. During esmolol infusion, there was no statistically significant increase of pulmonary capillary wedge pressure or PR interval. All 5 patients who required early termination of infusion because of systolic blood pressure falling below 90 mm Hg recovered within 30 minutes of stopping esmolol.

No patient developed symptomatic bronchospasm or initiation or exacerbation of congestive heart failure. No patient developed atrioventricular conduction abnormalities while on esmolol. Fourteen patients who completed the maintenance infusion of esmolol

were started on conventional oral β blockers. All patients tolerated oral β blockers without developing symptomatic adverse reactions.

The results of this study suggest that esmolol is safe and effective in lowering heart rate and arterial pressure (and hence rate-pressure product) in patients with acute myocardial ischemia and infarction and that the hemodynamic effects are rapidly reversed after termination of the infusion. In patients with acute ischemia in whom there is a desire to reduce oxygen demand, but concern that β blockade may precipitate heart failure, bronchospasm, conduction abnormalities or hypotension, esmolol may be safer to use than conventional longer-acting β blockers.

In summary, β blockers have been shown to be beneficial in the treatment of acute myocardial ischemia and have been shown to reduce mortality when administered long-term after acute myocardial infarction. Their effect on myocardial infarct size remains controversial. The ultrashort-acting β blocker esmolol may be an ideal drug to use in patients with myocardial ischemia in whom a reduction of heart rate is desirable but in whom there is concern that β blockers might not be tolerated. This agent has been shown to reduce experimental myocardial infarct size in reperfusion protocols and to improve recovery of the stunned myocardium. Clinical studies suggest that esmolol is effective in reducing heart rate of patients with ischemia and that its effect on heart rate is rapidly reversed after termination of drug infusion.

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Discussion

Dr. Sonnenblick (Bronx, New York): I might ask you the first question. Might you be mixing 2 endpoints? One is infarct size and the other is whether one can subdue active ongoing ischemia, such as unstable angina? The MILIS study was quite negative and I think very disappointing, and even the metoprolol repeat MIAMI study came out negative. In the face of that, one has to worry about being able to reduce infarct size metabolically. On the other hand, I do not think there is much argument among most people that unstable angina, when stabilized, has probably saved some myocardium basically by avoiding an impending infarction. With that in mind, did you see a clinical benefit in that patients had less chest pain and electrocardiographic changes than occurred during an unstable state? In other words, it is nice to have a decrease in heart rate and blood pressure, and if it is tolerated safely, I think that is a very nice benefit. However, was there a clinical benefit of esmolol that you could say was easily demonstrable either by chest pain, electrocardiographic changes or your clinical assessment of the patient?

Dr. Kirshenbaum (Boston, Massachusetts): In this preliminary study, clinical efficacy as determined by either a reduction in infarct size or a decrease in frequency or severity of ischemic episodes was not specifically measured. However, our impression was that esmolol did in fact provide a clinical benefit to the patients. We had 8 patients on intravenous nitroglycerin at the initiation of the β blockade because they had episodes of chest pain during the preceding 24 hours. In 6 of those 8 we had to terminate the intravenous nitroglycerin during the esmolol infusion because of the blood pressure response. None of these 6 patients had subsequent ischemic events during the esmolol infusion. At the end of the study when we turned the esmolol off, only 1 of those patients went on to have another episode of chest pain requiring reinstitution of intravenous nitroglycerin. All of these 8 patients were started on oral β blockers. In all 19 patients, only 2 had esmolol discontinued because of hypotension associated with an acute ischemic event. One patient had an evolving acute anterior myocardial infarction; the other patient developed a postprandial vagal eqisode associated with a fall in blood pressure and angina. I have no data on the frequency of ischemic events in the hours immediately before esmolol infusion and so I cannot comment on whether esmolol actually caused a reduction in the number of ischemic events. But at least in the 19 patients, the vast majority had no ischemic episodes during their esmolol infusion. In 1 patient, in fact, who had the esmolol terminated according to protocol and metoprolol started, there was a delay in starting the metoprolol between the house officer writing the order and the nurse fulfilling it. During that time, the patient had an ischemic episode with acceleration of her heart rate. She had clear angina during that time. So it is clinically suggested that during esmolol we are preventing the increase in oxygen demand and that minimizes the episodes of ischemia. Thus, it is clinically suggested that esmolol's ability to lower myocardial oxygen demand via reduction in heart rate-blood pressure product has the potential for reducing angina.

Dr. Morganroth (Philadelphia, Pennsylvania): Because of this experience, do you now, or would you if you could, routinely use esmolol in every patient in the coronary care unit who has active ischemia? If not, in whom would you be more cautious with the agent except for the obvious issues of heart block or overt heart failure?

Dr. Kirshenbaum: If I had a patient with symptomatic ischemia with a resting heart rate >75 beats/min and systolic pressure >110 mm Hg in whom I felt augmented myocardial oxygen demand was contributing to angina, I think it would be prudent to begin esmolol.

Dr. Morganroth: Do you place all patients with asymptomatic infarction or uncomplicated infarction in their first day on intravenous β blockers?

Dr. Kirshenbaum: No.

Dr. Morganroth: None of them, or if some, which patients?

Dr. Kirshenbaum: The initiation of β blockade in the acute infarct setting where patients are asymptomatic is presumably going to be done to reduce infarct size or to prevent against further eqisodes of ischemia. The data supporting β blockers for infarct reduction are not yet firm; thus, we do not aggressively initiate such medication in an asymptomatic patient. On the other hand, the available evidence certainly supports the use of β blockers in post–myocardial infarction patients for prevention of subsequent myocardial infarctions or sudden death. Thus, we routinely place patients without contraindications during their early post–myocardial infarction recovery period on oral β blockers.

Dr. Morganroth: But, you know, the intravenous metoprolol data are such that those patients received the drug on admission, or as close to admission as possible, and they had a 90-day mortality rate that was clearly less than those who received placebo on admission.

Dr. Kirshenbaum: Yes, but that was not confirmed in the MIAMI data and their long-term mortality was no different whether the drug was given at the start or at the end of admission. I am not by any means trying to claim that esmolol or any of the β blockers are infarct-limiting.What is important in the metoprolol study is that 47% of the patients who came in were excluded by the study's entry criteria. In the 3 large post–myocardial infarction β-blocker trials, 18 to 20% of patients were excluded at the onset because of potential adverse reactions to β blockers. Now some of those people were excluded because their heart rates and blood pressures were already low; in others there was a fear of producing bronchospasm, atrioventricular block, etc. It is in this subset of patients that esmolol may be particularly useful in defining a cohort that could safely tolerate β blockers, despite a prior history of bronchospasm, conduction system disease, etc. The ability to tolerate esmolol could then select patients who could be safely started on longer acting β blockers. This would add β blockers' proven long-term preventive benefit to post–myocardial infarction patients who currently are routinely excluded from β blockers. If they

tolerate esmolol, they should tolerate an oral agent, and that hopefully is where esmolol is special.

Dr. Sonnenblick: In patients with unstable angina, with a large amount of myocardium at risk, do you think there is a subgroup in whom you could show that when giving the β blocker, you will find the end-diastolic pressure rising and the output decreasing, which indicates perhaps that the tachycardia is due to a huge infarct—as opposed to another group where if the filling pressure falls, you have showed a benefit on the ischemia and that you ought to press ahead more vigorously with a β blocker? Have you seen that differential?

Dr. Kirshenbaum: Our patient population was too small to prove this very logical assumption. I suspect most patients with severe unstable angina at rest have markedly diminished myocardial blood supply, secondary to fixed coronary obstruction, with concomitant coronary spasm or thrombosis, rather than acute increase in myocardial oxygen demand. However, if their instability is accompanied by persistent elevations in heart rate or blood pressure, then I strongly suspect that a reduction of myocardial oxygen demand would help alleviate angina.

Dr. Lowenthal (Philadelphia, Pennsylvania): In the clinically stable patient who has had a myocardial infarction and who has had a good response to esmolol, would you consider starting an oral β blocker during the maintenance period so that when the infusion has been discontinued, there will not be any risk of rebound and the patient will be adequately covered? Have you had that experience?

Dr. Kirshenbaum: We did not have that experience because all of our patients were started on oral agents following the termination of the esmolol. One patient had delay in receiving oral metoprolol after esmolol infusion and experienced an ischemic episode in the interim associated with tachycardia.

Dr. Lee (McGaw Park, Illinois): In the patients who became hypotensive, did the peripheral resistance decrease?

Dr. Kirshenbaum: While we did not calculate the peripheral resistance during the hypotensive episodes, I suspect it was lower. However, the relative contributions to the hypotension from a reduction in cardiac output versus a reduced peripheral resistance are unknown.

Dr. Lee: I think that's an important issue—whether they were hypotensive because of vasodilation or because of reduced cardiac output.

Dr. Sonnenblick: In the data that he showed, the cardiac output, if anything, with time was rising at the time the blood pressure was falling. That leaves you the resistance to work with, so that would imply that the resistance had fallen somewhat further. But you also have volume problems in these patients that are on nitroglycerin as well, so it is a complex problem. If there are no further questions, I want to thank Dr. Kirshenbaum. These are difficult experiments to do and he has opened a whole area—both infarct reduction and also the safe and effective way to acutely test the problem. Thank you.

Use of Esmolol in Hypertension After Cardiac Surgery

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Systolic hypertension, which is common soon after cardiac surgery, increases cardiac work and may threaten fresh vascular anastomoses. Because postoperative hypertension is often associated with elevated catecholamines and preoperative use of β-blocking agents, esmolol, an ultrashort-acting β-blocking agent, was compared with nitroprusside in a crossover study in this setting. Twelve patients, 18 to 28 hours after cardiac surgery (coronary artery bypass graft in 9, aortic valve replacement in 2 and valved aortic conduit with reimplantation of coronary arteries in 1 patient) received controlled infusions of esmolol (mean dosage 142 ± 100 μg/kg/min, range 50 to 300 μg/kg/min) and nitroprusside (mean dose 1.6 ± 1.3 μg/kg/min, range 0.5 to 2.75 μg/kg/min). In this open-label study, choice of the first drug was randomized, after which patients were then crossed over to the other study drug. Therapeutic response (≥15% systolic blood pressure reduction) was achieved in 11 of 12 esmolol patients and 12 of 12 nitroprusside patients. Both drugs significantly lowered systolic and diastolic blood pressure, as well as left ventricular stroke work index. While the cardiac index was decreased by esmolol and increased by nitroprusside, neither drug significantly changed stroke volume index. Systemic vascular resistance, unchanged by esmolol, was decreased significantly by nitroprusside. Oxygen saturation and Pao_2, unchanged with esmolol, were both significantly reduced with nitroprusside. Thus, for hypertension early after cardiac surgery, esmolol is safe, effective and rapid and, compared with nitroprusside, results in less unwanted decrease in diastolic blood pressure and oxygen saturation, but there is more decrease in heart rate and cardiac index.

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Hypertension, occurring in the early hours after open heart surgery, is common and may be quite troublesome. Its occurrence is particularly untimely as fresh vascular anastomoses may be threatened, and increasing demands are placed on a myocardium just beginning to recover from ischemic insult. Even more serious complications may arise in the patient recognized at surgery to have an atherosclerotic, thin-walled, tenuous aorta or a recently repaired or coexistent aortic dissection. The clinical situation in these patients may be one of hyperdynamic circulation with increased heart rate and cardiac output. Very often systolic blood pressure elevations predominate with normal or even subnormal diastolic levels.

Patients rapidly and completely withdrawn from preoperative β-blocking agents, as well as those previously hypertensive, are particularly subject to this occurrence. The documentation of elevated circulating catecholamine levels early after open heart surgery has figured prominently in the proposed mechanism of this complication.[1–5] Many investigators have demonstrated a several-fold increase over preoperative levels of epinephrine, which may last for 2 to 3 days. Elevations of serum norepinephrine levels are less striking but may persist for several days postoperatively. It has also been suggested that extracardiac sympathetic activity may contribute to vasoconstriction or release of norephinephrine from postsynaptic junctions.[6] Alterations in serum renin and aldosterone levels have also been implicated but have been less completely studied.

Various definitions of postoperative hypertension have been used. Flaherty et al[7] suggested that a sudden and persistent increase in mean arterial pressure of 20 mm Hg or more, with a mean arterial blood pressure of at least 95 mm Hg, was indicative of this phenomenon, and found that 61% of patients undergoing coronary bypass surgery at their institution met this criterion. Fremes et al[8] proposed a mean arterial pressure of at least 105 mm Hg and 42% of their coronary bypass patients met this definition. Considering

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that an estimated 191,000 bypass surgeries were performed in 1983,[9] one can appreciate the magnitude of this clinical problem.

Except in previously hypertensive persons, the natural history is usually a benign one, with gradual resolution of hypertension over the first 2 to 3 postoperative days. Because of its limited duration and the fact that, initially, patients requiring therapy are anesthetized, often intubated and unable to take oral medications, therapy is almost always intravenous. Some, but not all, patients must then be weaned to oral medications, which may be prescribed for several postoperative days. Initial therapy is most commonly sodium nitroprusside,[8] with recent interest in nitroglycerin.[7] Other intravenous antihypertensives, such as hydralazine, methyldopa and even chlorpromazine, are often used as well. Unfortunately, these agents are not well suited for treatment of systolic hypertension; in some cases they add to the tachycardia and hyperdynamic circulatory state and may produce hypoxemia. Beta-blocking agents have potential value, but have been used infrequently because of the traditional nonavailability of intravenous infusion and the relatively slow onset and offset of action, should adverse effects arise.

For these reasons, we compared esmolol, an ultrashort-acting β-blocking agent, and nitroprusside, the standard form of therapy for postoperative hypertension.

Methods

Patient selection: Systolic blood pressure of at least 140 mm Hg was required. We chose a systolic blood pressure criterion because systolic hypertension appears to predominate in this condition, and also because of inaccuracies known to exist in algorithms for determination of mean arterial blood pressure from analog signals. Additionally, patients had to be between 18 and 75 years old and able to give informed consent. All patients had to have a functioning balloon flotation catheter with pulmonary capillary wedge pressure <18 mm Hg. Heart rate had to be >70 beats/min and the cardiac index >2.2 liters/min/m^2, with a stroke volume index >25 ml/beat/m^2. Criteria for exclusion included pregnancy, atrioventricular block greater than first degree, sick sinus syndrome without a functioning pacemaker, chronic obstructive pulmonary disease severe enough to preclude the use of a β-blocking agent or active bronchospasm. In addition, patients receiving other experimental drugs within the past 2 weeks and those with significant impairment of renal or hepatic function were excluded.

Patient description: Twelve hypertensive patients, 5 men and 7 women, were studied. The mean arterial pressure before esmolol treatment was 103 mm Hg; before nitroprusside, it was 106 mm Hg. Average age was 65 ± 10 years (range 43 to 74). The cardiac surgical procedure consisted of isolated coronary bypass grafting in 9 patients, with aortic valve replacement in 2 patients, and insertion of a valved conduit replacement of the aortic root with reimplantation of the coronary arteries (the Bental procedure) in 1 patient.

Preoperatively, 6 patients had received β-blocking medications, and 6 had a history of preoperative hypertension. Preoperative left ventricular angiographic ejection fraction was 70 ± 22% and left ventricular end-diastolic pressure was 16 ± 3 mm Hg. The number of hours in the intensive care unit before study was 23 ± 3 hours.

Operative procedure: Anesthetic medications included intravenous Fentanyl and diazepam, with supplemental nitrous oxide and halothane as needed. Cardiopulmonary bypass was performed using a bubble oxygenator, and myocardial preservation used the technique of hypothermic, hyperkalemic cardioplegia. Mean cardiopulmonary bypass time was 140 ± 51 minutes, ischemic aortic cross-clamp time was 90 ± 43 minutes and the lowest esophogeal temperature achieved was 22 ± 2°C. The number of grafts inserted per patient was 3.5 ± 0.9.

Protocol: After identification of the patient and procurement of informed consent, a prestudy period was entered during which physical examination, medical history, blood and urinalysis as well as an electrocardiogram were obtained. If previously treated for postoperative hypertension, as was the case in all patients, medication was weaned and discontinued 20 minutes before beginning the study. Patients were then randomized to receive either esmolol or nitroprusside as their first treatment drug. After randomization, baseline hemodynamic and laboratory data were obtained. If randomized to esmolol, the first titration began with a loading infusion of 500 μg/kg/min for one-half minute. Following this, 25 μg/kg/min was administered for 4 minutes. Subsequent increases in titration dosage were at 50 μg/kg increments and were preceded by 1 full minute loading infusion. The maximum dosage allowed under this protocol was 300 μg/kg/min. If randomized to nitroprusside, the first titration began at a dosage of 0.5 μg/kg/min for 2 minutes. The second titration was at 0.75 μg/kg/min, but all subsequent increases in dosage were at 0.5 μg/kg/min increments. The maximal allowable dosage was 10 μg/kg/min.

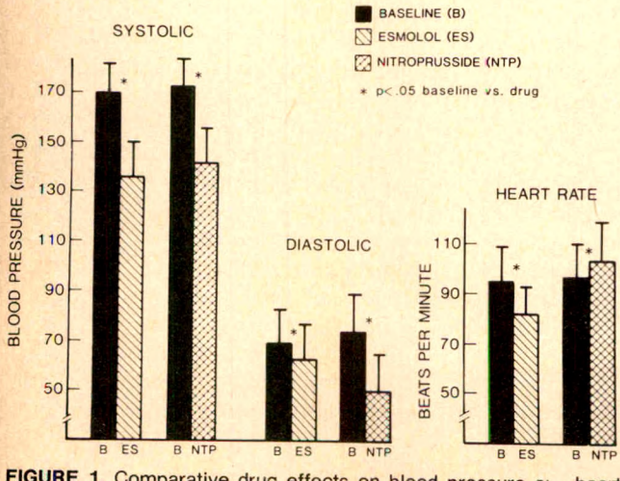

FIGURE 1. Comparative drug effects on blood pressure and heart rate.

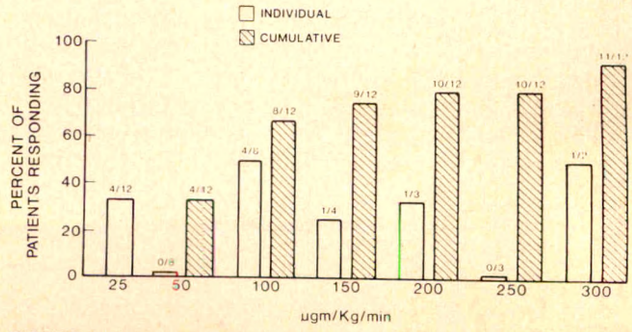

FIGURE 2. Dose response with esmolol (≥15% systolic blood pressure reduction).

TABLE I Postoperative Hypertension Study Results

	Esmolol			Nitroprusside		
	Baseline	Drug	Δ%	Baseline	Drug	Δ%
Blood pressure						
Systolic (mm Hg)	170 ± 12*	136 ± 14	−20%	173 ± 11*	141 ± 15	−18%
Diastolic (mm Hg)	69 ± 14*	63 ± 14	− 8%	72 ± 15*	50 ± 15	−31%
Heart rate (beats/min)	95 ± 9*	82 ± 11	−14%	97 ± 14*	104 ± 15	+7 %
Responders						
>15% SAP		11/12			12/12	
SAP ≤120 mm Hg		1/12			3/12	
DAP ≤50 mm Hg		1/12			7/12	

* p <0.05 baseline vs drug.
DAP = diastolic arterial pressure; SAP = systolic arterial pressure.

The titration period for each drug was ended when certain criteria had been met. Reaching either a 15% decrease in systolic arterial pressure or a systolic pressure of ≤120 mm Hg constituted efficacy criteria. Heart rate <60 beats/min, systolic arterial pressure <90 mm Hg or reaching the maximal allowable dosage of either drug constituted safety endpoints. After the treatment endpoints had been reached, repeat hemodynamic measurements were obtained after 20 minutes of steady-state infusion. A 20-minute washout period followed, and the patients were then crossed over to the other drug for a repeat of the titration sequence.

Data analysis: All data are reported as mean ± standard deviation. A paired *t* test analysis was performed to determine significant differences, which were deemed present when p values were <0.05.

Results

A summary of results is listed in Table I. Systolic arterial pressure was decreased with esmolol from 170 ± 12 to 136 ± 14 mm Hg, representing a 20% decrease. With nitroprusside, systolic pressure was decreased from 173 ± 11 to 141 ± 15 mm Hg, an 18% decrease. Both of these changes are statistically significant. Diastolic pressure with esmolol was reduced from 69 ± 14 to 63 ± 14 mm Hg, an 8% decrease, and with nitroprusside from 72 ± 15 to 50 ± 15, a 31% decrease, both of which are statistically significant. Heart rate with esmolol was reduced from 95 ± 9 to 82 ± 11 beats/min, a 14% decrease; in contrast, nitroprusside resulted in a 7% increase, from 97 ± 14 to 104 ± 15 beats/min. Eleven of 12 patients with esmolol, and all of the nitroprusside patients, met the 15% systolic arterial pressure reduction criterion, and therefore were responders. One of 12 esmolol patients and 3 of 12 nitroprusside patients achieved a systolic arterial pressure <120 mm Hg. Diastolic arterial pressure <50, possibly an adverse effect, was seen in 1 esmolol patient and 7 of 12 nitroprusside patients. The blood pressure and heart rate data are illustrated in Figure 1.

Figure 2 illustrates the dose-response relation with esmolol. At 25 μg/kg/min, 4 of 12 patients (33%) achieved the desired blood pressure response. At 100 μg/kg/min, 8 of 12 patients (66%) were cumulative responders. Two additional individual patients, 1 at 150 and the other at 200 μg/kg/min, respectively, were added to the cumulative responders, and at the maximal dosage level of 300 μg/kg/min, the last additional patient became a responder. These data suggest that control of hypertension with esmolol may require higher dosage levels. This is in contrast to the experience with esmolol in the treatment of supraventricular tachyarrhythmias, where most potential responders do so at the dosage of ≤150 μg/kg/min.[10]

Figure 3 illustrates the individual systolic blood pressure responses to various dosages of esmolol. Virtually all patient responses are consistent and predictable and further reductions in blood pressure occur with progressively higher esmolol dosage. Patient no. 11, at the top of the figure, was the only nonresponder to esmolol and appears to be identifiable because of the uniquely high blood pressure before therapy.

The effects of the 2 study drugs upon cardiac filling pressures are shown in Figure 4. In the left panel, right

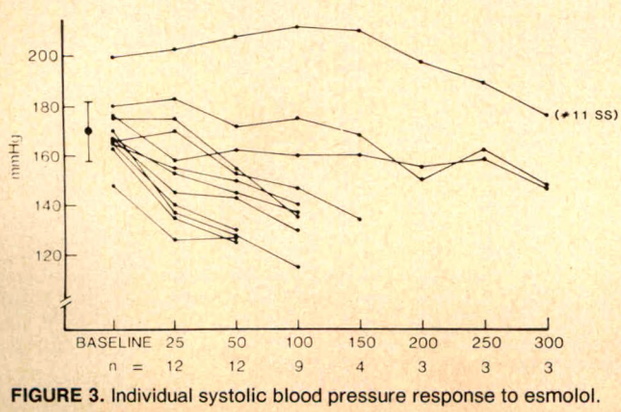

FIGURE 3. Individual systolic blood pressure response to esmolol.

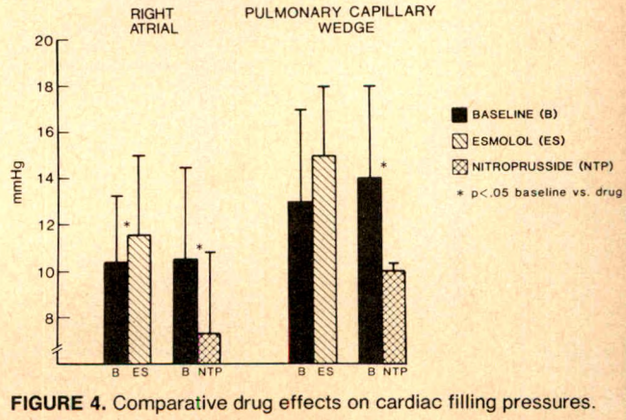

FIGURE 4. Comparative drug effects on cardiac filling pressures.

Discussion

Dr. Lowenthal (Philadelphia, Pennsylvania): Dr. Gray, what was your mean level of PaO_2 reduction with the nitroprusside?

Dr. Gray (Los Angeles, California): The mean PaO_2 level went from 118 to 72 mm Hg.

Dr. Lowenthal: Would you postulate the mechanism to be shunting?

Dr. Gray: That's the general feeling. This finding has been demonstrated by many people, and the basic idea is that there is paralysis of the usual hemostatic control areas, so there is general paralysis of local precapillary regulation of blood flow.

Dr. Lowenthal: Do you think that is augmented at all through bypass and the various hookups during coronary artery bypass grafts?

Dr. Gray: I don't know whether there is the same degree of change, but this PaO_2 decrease has also been demonstrated in the intensive care setting with both medical intensive care unit patients and post–myocardial infarction patients who have been monitored hemodynamically. The decrease we showed may be more dramatic than in the intensive care unit patient, but is something that we encounter very often in the management of these patients. It is a reasonably serious and frequently noted phenomenon.

Dr. Lowenthal: Usually during the routine hypertensive encephalopathy, with no extracorporeal hookup, a substantial fall in PaO_2—say, from 100 to 70—is unusual. I don't know whether it is caused by the conversion to cyanide and thiocyanate. But, one of the hemodynamic spin-offs of this is whether or not the fall in PaO_2 could in part be related to the higher heart rate response that you see, and that it's not all a vascular effect of nitroprusside.

Dr. Gray: We measured oxygen delivery per pulse, and it also diminishes with nitroprusside so I don't think that's the explanation. I think we have to keep in mind that all the patient groups in which nitroprusside-induced hypoxemia has been documented have some element of cardiopulmonary/physiologic derangement. These are not people off the street with, as you say, a hypertensive encephalopathy or some noncardiopulmonary reaction.

Dr. Lowenthal: This is fascinating. Let me direct the next question to you, Dr. Reves, and we can discuss it. It is possible that this fall in PaO_2 could be due to blunting by the concomitant administration of trimethaphan with nitroprusside? That's been advocated in an attempt to block formation of the cyanide and thiocyanate.

Dr. Reves (Durham, North Carolina): Let me answer your first question about whether or not the drop in PaO_2 is related to cardiopulmonary bypass. I don't think it is. We just finished a study looking at shunt fractions immediately after bypass. We looked at the duration of bypass and all sorts of vasoactive compounds, and, in fact, sometimes a shunt fractioning improved after cardiopulmonary bypass. I think it's a real effect of sodium nitroprusside in this group of patients, the etiology of which I do not know. But I don't think the drop in PaO_2 is affected by cardiopulmonary bypass per se. Trimethaphan used to be the number 1 drug for postoperative hypertension, but I don't remember what happens to shunt data in those patients.

Dr. Sonnenblick (Bronx, New York): One of the questions I would ask is the problem of interpreting contractility or stroke work when you have the blood pressure falling. You might plot it as stroke volume versus pulmonary capillary wedge, because the fall in stroke work is going to be so dominated by the change in blood pressure that it doesn't really reflect the Starling-type curve that you're trying to plot. It would probably look somewhat the same, but it would be interesting to see what it looks like as a stroke volume plot.

Dr. Gray: It is obviously a question similar to the problem of the chicken and the egg—as the heart has less demand placed upon it because of the lower blood pressure, it's doing less work—but is it doing less work because it has been paralyzed in some way, or is it simply because the afterload is reduced?

Dr. Sonnenblick: I think the problem there is that you can change the work all over the lot by changing the blood pressure, independent of anything else, so it complicates the interpretation. You have got to remember the Sarnoff curves really were only stroke work curves, because blood pressure was held constant, so it's really a stroke volume curve with a constant blood pressure. As soon as you change the blood pressure, you can really make the curves move around significantly.

Dr. Gray: One can construct it here, just simply using the available data. The stroke volume with nitroprusside has absolutely no change. The wedge pressure falls from 14 to 10, so you would see a downward movement or one suggesting an improved functional status with nitroprusside, the traditional vasodilator response shifting to a new curve. The stroke volume index with esmolol has no statistically significant change, the number goes from 28 to 27 and the wedge pressure goes up a very small amount, from 13 to 14, so we would see a more or less static situation with regard to inotropic influence.

Dr. Sonnenblick: I would just like to extend another interpretation. Everything that you have shown says postbypass hypertension is a somewhat unique form of hyertension in that you really seem to have a cardiac-caused hypertension. In other words, you've got an increase in blood pressure that seems to be related to your cardiac output independent of the peripheral resistance. Is that perhaps related to the postperfusion hypothermia recovery period?

Dr. Gray: Well, I think the implication of your question is that we don't know what causes this hypertension. From interpreting our data, I would urge others to look at their own data in this regard; we don't normally expect to see a marked increase in systemic vascular resistance. In some patients, of course, it is quite high, there is no doubt about it. I don't want to imply that this drug is the only answer to this type of problem, because nitroprusside is better in some other patients. However, esmolol does seem to have kind of a mixed hemodynamic profile with very normal systemic re-

sistance, slightly elevated cardiac index, moderately high systolic blood pressure and relatively normal diastolic blood pressure.

Dr. Lowenthal: To support your contention, I think the fact that systemic resistance is basically normal and diastolic pressure is likewise normal, would tend to negate the contention that the renin angiotensin system is playing a major role here. Even though catecholamines may be elevated and innervention into the juxta-glomerular apparatus can stimulate renin production, it's probably not playing a major role.

Dr. Sonnenblick: So it rather supports the contention initially that the postoperative hypertension was caused by a catecholamine surge that was cardiac stimulating. It looks very much like the type of hypertension you get from stellate stimulation.

Dr. Gray: I don't have the results yet, but renin and epinephrine/norephinephrine levels were sent to the laboratory.

Dr. Iskandrian (Philadelphia, Pennsylvania): Was the pericardium left open, I assume, after the operation?

Dr. Gray: Our surgeons generally just open the pericardium in the inverted T and leave it open.

Dr. Iskandrian: That's fascinating; that's the first time we will see the effect on the intracardiac hemodynamics with an open pericardium. All the studies so far have been with intact pericardium. It is interesting that, even when the pericardium is open, you still see a slight elevation of the wedge pressure. One can only postulate that if the pericardium was not open, whether the elevation in wedge pressure would have been higher.

Dr. Lee (McGaw Park, Illinois): I am interested in your observation that the hypertension occurs within 1 or 2 hours after surgery. What is the time course of postbypass hypertension? Is it fairly stable and how long can one expect it to last?

Dr. Gray: This particular group of patients usually emerges from the operating room hypertensive, and all of our study patients were on some antihypertensive agent initially. However, because we have to get an informed consent, we did wait until the patient could give it to us. It might be argued that 24 hours later is still not a proper time to obtain a real informed consent on a patient, but that is the reality. So we have certain constraints. The patients were all studied on the average of 23 hours after the surgery, and the range is rather narrow—18 to 26, I think. At the end of the titration period, we made our recordings. We made a clinical decision at the end of the comparison as to what drug the patient should be put on, and in some patients it was esmolol, and in a few patients it was nitroprusside; mostly it was esmolol. We did treat the patients for anywhere from an hour and 10 minutes to 23 hours with esmolol—an average of just over 6 hours.

Dr. Morganroth (Philadelphia, Pennsylvania): What problems do you see with designing a protocol to clear up the confusion about the first 23 hours by actually having obtained informed consent before operation on all patients, and then allowing the anesthesiologist to start the drip of either nitroprusside or esmolol in the operating room? It seems to me that would be a more rigorous design to answer this question.

Dr. Gray: I see many problems. It would be very difficult to design such a protocol.

Perioperative Use of Esmolol

J. G. REVES, MD, and PAOLO FLEZZANI, MD

Stressful surgical stimuli, such as endotracheal intubation, surgical incision, organ manipulation and emergence from anesthesia, elicit adrenergic responses that precipitate transient but intense increases in heart rate and blood pressure. Although this response is well tolerated in healthy patients, patients with ischemic heart disease are at significant risk of myocardial ischemia and infarction owing to the sudden increase in myocardial oxygen demand. Parenteral β blockers are effective in blunting this adrenergic response, but the duration of action of these agents is long-lasting and the degree of β blockade is often difficult to predict. Further, long-acting parenteral β blockers may cause adverse effects, the reversal of which presents a difficult clinical problem in patients with ischemic heart disease. The availability of esmolol, an ultrashort-acting parenteral β-adrenergic antagonist with a half-life of 9 minutes, brings obvious advantages to the perioperative management of hypertension and tachycardia. With esmolol treatment, the difficulties of therapy with long-lasting β blockers are avoided. Also, to blunt the adrenergic response, the anesthesiologist will have an alternative to increasing the depth of anesthesia, which can accentuate cardiovascular depression and prolong awakening and postoperative respiratory depression. Clinical studies performed during the perioperative period reveal that esmolol is safe and effective in this setting. Esmolol has been shown to be safe and efficacious in patients in ASA classifications I through IV and patients undergoing carotid endarterectomy and coronary artery bypass surgery. The pharmacokinetic profile, rapid onset and elimination half-life make this agent particularly well suited to treat the very intense but transient adrenergic responses to surgical stress in patients undergoing cardiac and noncardiac surgery.

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Esmolol is a fast-acting and ultrashort-lasting β_1-adrenergic antagonist[1] that has potential for use in the perioperative period. A drug that can quickly control tachycardia and minimize hypertension without prolonged negative chronotropic and inotropic effects is ideal for the treatment of transient episodes of hemodynamic hyperactivity that occur during anesthesia. Stressful stimuli such as endotracheal intubation, surgical incision and manipulation, cardiopulmonary bypass and emergence from anesthesia elicit adrenergic responses that cause transient increases in heart rate and blood pressure.[2] Although tachycardia and hypertension are well tolerated in most patients, they can lead to myocardial ischemia and myocardial damage in patients with ischemic heart disease undergoing cardiac surgery.[3]

The safe use of β-adrenergic antagonist drugs in the perioperative period is well established.[4] The continued administration of propranolol and other β-adrenergic antagonists is associated with less severe intraoperative hemodynamic instability[5–8] and continued administration avoids the potential hazards of abrupt withdrawal.[9] However, β-adrenergic antagonists can add to the effects of some anesthetics that also produce vasodilation, cardiac depression and decreased heart rate and interfere with normal homeostatic reflexes.[10–22] The availability of an effective but short-lasting β-adrenergic antagonist brings an obvious advantage in anesthetic management because it obviates the need to use either long-lasting β-adrenergic antagonists or the requirement to increase depth of anesthesia, which can accentuate cardiovascular depression and prolong awakening and postoperative respiratory depression. This is particularly a concern in short operations and when the stressful stimuli are brief. Advantages of esmolol compared with other parenteral β antagonists (propranolol and metoprolol) are predictability, rapid onset and short duration of action. Compared with the noncardioselective drug propranolol, a lower likelihood of development of postoperative hypertension secondary to unopposed α-receptor stimulation[23] is another potential advantage of esmolol.

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TABLE I Esmolol During Anesthesia: Multicenter Studies

ASA class I–IV	185 patients	Safe, effective; attenuates tachycardia and hypertension during intubation
Carotid endarterectomy	74 patients	Safe, effective; attenuates tachycardia and hypertension during intubation
Coronary artery surgery	102 patients	Safe, effective; attenuates tachycardia and hypertension during intubation and surgical stress

ASA class I = no organic, physiologic, biochemical or psychiatric disorder; II = mild to moderate systemic disturbance or disease; III = severe systemic disturbance or disease; IV = life-threatening systemic disturbance or disease.

Laboratory Investigation

Dog studies have examined the effects of esmolol infusion with clinically relevant general anesthetic agents.[24,25] In dogs anesthetized with 2.2% end-expired enflurane (1 MAC), esmolol given for 20 minutes at infusion rates of 0, 100, 300, 1,000 and 3,000 μg/kg/min produced dose-related decreases in heart rate, left ventricular contractile force and blood pressure.[24] Decrements in contractile force were greater than heart rate, suggesting a more pronounced additive negative inotropic effect than negative chronotropic effect. Cardiac output was preserved until the highest doses of esmolol were given. Increases in heart rate after isoproterenol administration (1 μg/kg) were totally blocked with doses of 300 μg/kg/min of esmolol, yet blood pressure decreased, indicative of the β_1 selectivity of esmolol. Because β_1 blockade was complete at 300 μg/kg/min, but 1 dog died at 1,000 μg/kg/min and the other 4 dogs at 3,000 μg/kg/min, the safety margin appears to be relatively small in the enflurane-anesthetized dogs given esmolol. This is consistent with other data that show that enflurane and a β-adrenergic blocker (propranolol)[14] are a potent negative inotropic combination. However, enflurane appears to produce no greater hypotensive effect than halothane when both are combined with esmolol.[25] The hemodynamic depression caused by esmolol is significantly enhanced by inhalation anesthetics; both halothane (1.5%) and enflurane (2.2%) produced marked hypotension compared with esmolol in the same awake dogs. The clinical implication of these data is that esmolol administered to anesthetized patients may be expected to accentuate hemodynamic depression, but at effective doses (doses that block isoproterenol-induced increases in heart rate), hemodynamic stability is preserved.

Human Investigation

Published clinical studies have primarily dealt with 2 issues: the safety of esmolol in anesthetized patients and the efficacy of esmolol in blocking tachycardia and hypertension during the induction of anesthesia and tracheal intubation.[26–29] Three multicenter studies have investigated the safety and efficacy of esmolol in anesthetized patients undergoing carotid endarterectomy, coronary artery surgery and multiple, noncardiac surgical procedures (Table I); the results have not yet been published.

The hemodynamic effects of esmolol in anesthetized humans depend on several factors besides its

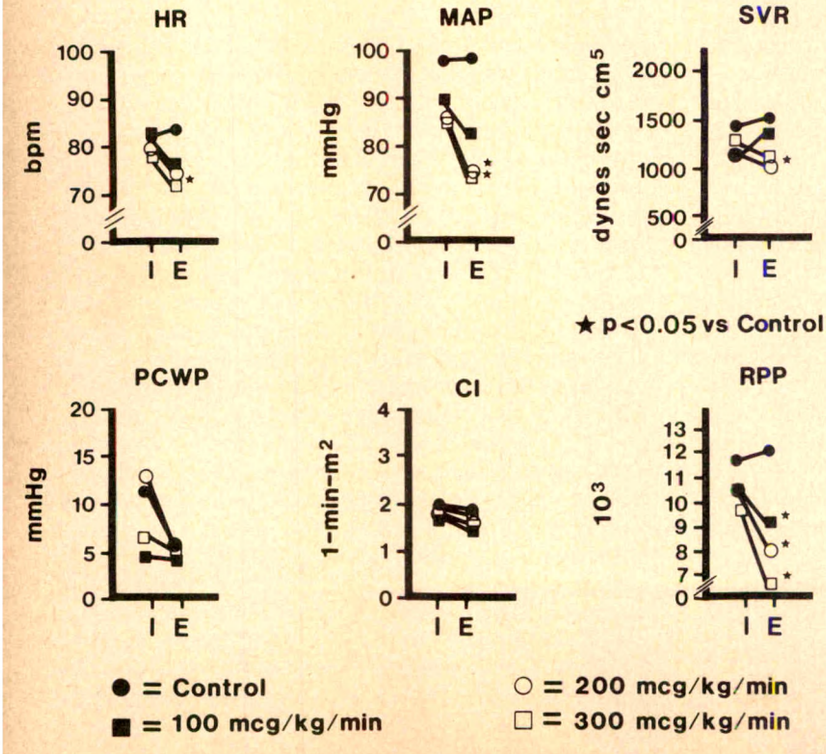

FIGURE 1. Hemodynamic effects of esmolol in patients anesthetized with diazepam, 0.5 mg/kg, N_2O:O_2 (50:50) and pancuronium, 0.1 mg/kg. Heart rate is significantly ($p < 0.05$) lower in esmolol-treated patients than in untreated control subjects. Esmolol 100 = infusion of 500 μg/kg/min 1 minute, then 100 μg/kg/min for 3 minutes; esmolol 200 = infusion of 500 μg/kg/min for 2 minutes, then 200 μg/kg/min for 2 minutes; and esmolol 300 = infusion of 500 μg/kg/min for 3 minutes, then 300 μg/kg/min for 1 minute. CI = cardiac index; E = esmolol infusion; HR = heart rate; I = induction of anesthesia; MAP = mean blood pressure; PCWP = pulmonary artery capillary wedge pressure; RPP = heart rate–systolic blood pressure product; SVR = systemic vascular resistance. Data from Menkhaus et al.[26]

intrinsic β-antagonist activity: concurrent anesthesia, underlying sympathetic tone, concurrent vasoactive drug therapy, intensity of the stressful stimulations and patient cardiovascular status. Understanding these interactions is essential if the effects of esmolol are to be compared in studies that differ with regard to anesthesia (e.g., ketamine vs thiopental), pharmacologic therapy (patients who did and those who did not receive β blockers), time of esmolol administration (before vs after intubation) and patient disease (normal cardiovascular system vs patients with coronary artery disease).

The hemodynamic effects of 3 infusion rates of esmolol (100, 200 and 300 μg/kg/min after loading with 500 μg/kg/min) were studied in patients undergoing coronary revascularization and the results were compared with those in a similar population of untreated control subjects[26] (Fig. 1). After induction of anesthesia with diazepam (0.5 mg/kg) and before intubation, esmolol infused at rates >100 μg/kg/min significantly ($p < 0.01$) decreased the heart rate (10% below the control group values) and systolic and mean blood pressures (20% below control group values). Cardiac index, systemic vascular resistence, pulmonary capillary wedge pressure and left ventricular stroke work index were not statistically different between the groups. Under these conditions, esmolol decreased the rate-pressure product significantly ($p < 0.001$) compared with control values and displayed a dose-related trend that was not statistically significant.

Esmolol protects patients from hypertension and tachycardia. In 1 study of patients with coronary artery disease, 1 minute after intubation, the heart rate was significantly ($p < 0.001$) lower in all esmolol-treated groups (15% below control group values).[26] The same was true for systolic and mean blood pressure (10 to 15% below control group values), whereas no differences were found within the esmolol groups. Cardiac index and the derived hemodynamic measurements were unchanged, but the rate-pressure product was significantly ($p < 0.001$) decreased (>20% below control group values) with a weak dose-related trend. The increases in heart rate and blood pressure were associated with increases in norepinephrine levels in the control patients but not in the esmolol-treated patients (Fig. 2). Fifteen minutes after termination of esmolol infusion, all hemodynamic values (directly measured and derived) returned to baseline levels, demonstrating the short-lived hemodynamic effect of esmolol.

Menkhaus et al[26] found that esmolol was well tolerated, with only 1 episode of hypotension (systolic blood pressure <90 mm Hg) and no episodes of impaired atrioventricular conduction. In 1 patient in each of the 4 groups, ST-segment changes compatible with ischemia developed. Their study emphasizes that esmolol can be safely used in association with diazepam–nitrous oxide anesthesia and that esmolol is effective in blocking the hemodynamic response to stressful stimuli by means of β-adrenergic receptor blockade, as suggested by the simultaneous increased norepinephrine plasma concentration during intubation. It confirms the short-lived activity of esmolol and its potentially beneficial effect on global myocardial oxygen balance as represented by the rate-pressure product, although the fact that ST-segment changes occurred reemphasizes the concept that regional ischemia can occur in the presence of an adequate global myocardial oxygenation. Menkhaus et al did not find a statistically significant dose-dependent effect, presumably because a sufficiently wide dosage regimen was not used or because steady state was not achieved at each infusion dosage.

Girard et al[27] reported that when esmolol was used according to a similar dosage protocol in patients undergoing coronary revascularization and anesthetized with high-dose fentanyl (75 μg/kg) in oxygen, the heart rate and cardiac index measured during a stress-free period (after intubation and before incision) decreased significantly ($p < 0.05$), but in a fashion similar

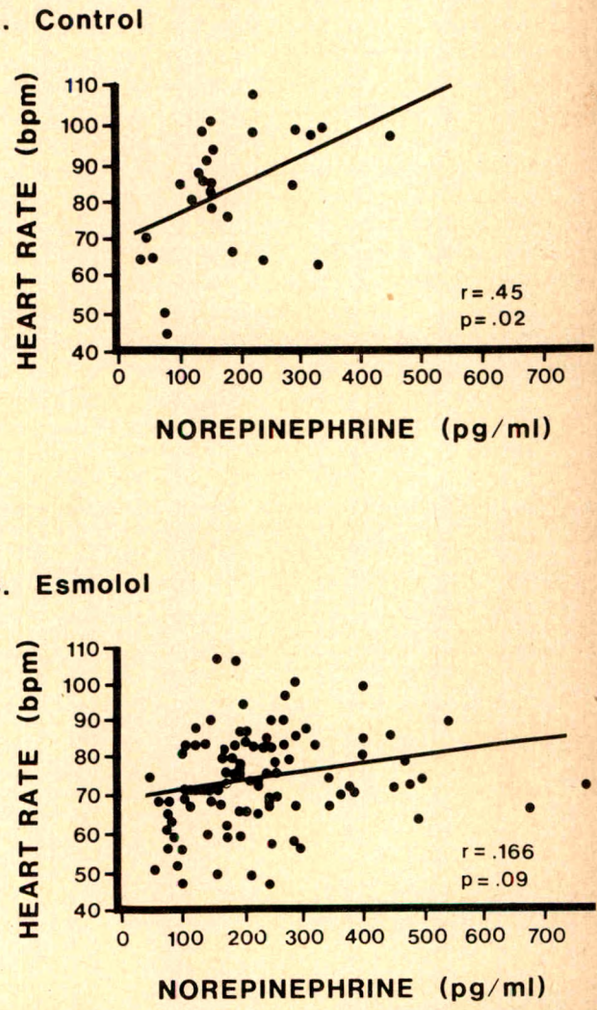

FIGURE 2. Heart rate (HR) and norepinephrine (NE) levels in patients with ischemic heart disease after endotracheal intubation. **A,** patients who did not receive esmolol; **B,** patients who received esmolol infusions of 100, 200 and 300 μg/kg/min. There is a weak but significant association between HR and NE in untreated patients, but a very poor association in the patients with β_1-adrenergic blockade with esmolol. This suggests β blockade of the adrenergic response to intubation.

to that in the control group. This study, while reconfirming the safety and short-lived action of esmolol (plasma level reached 8% of peak level 5 minutes after infusion and less than 2% of peak level after 30 minutes), emphasizes that concurrent factors, such as type and depth of anesthesia, intensity of stimulation and adrenergic response, affect the hemodynamic response.

Korenaga et al[28] investigated the effects of esmolol (500 μg/kg/min × 4 minutes followed by 300 μg/kg/min) during intubation in healthy patients given thiopental. The heart rate was lower (20% below control values) after intubation than in untreated control patients, as was systolic blood pressure (15% below control group values). In healthy patients anesthetized with ketamine,[29] esmolol (300 μg/kg/min × 10 minutes) was effective in decreasing heart rate and systolic blood pressure.

In summary, laboratory and clinical investigations indicate that esmolol is an effective β_1-adrenergic receptor antagonist that is well suited to attenuating the hemodynamic responses to stressful stimuli in the intraoperative period. Its pharmacokinetic characteristics (the rapid onset and elimination) make this agent particularly well suited for preventing and treating the adrenergic responses to intraoperative stresses, which can be very intense but often brief in duration.

Esmolol appears to be safe when used in combination with intravenous anesthetic agents; its marginal safety when used in combination with inhalation agents requires further investigation. Questions regarding the use of esmolol perioperatively in patients who are hypertensive, who have impaired ventricular function and who are receiving long-term β- and calcium-entry blocking therapies remain to be answered.

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Discussion

Dr. Sonnenblick (Bronx, New York): One of the things that most of us are impressed about is that the perioperative myocardial infarction rates, which used to be immensely high, are now vastly lowered by having the patients go to surgery on their β blockers. Do you think it is reasonable to say that the surgical patient is safer on a β blocker if he has a potentially threatened ischemic myocardium?

Dr. Reves (Durham, North Carolina): I think that is true. I think we learned from the experience when propranolol was withdrawn before surgery. This procedure ended up precipitating some angina and infarction even before the operation. One of the worst things that happened to us as cardiac anesthetists was the introduction phase of calcium-channel blockers. When these drugs first appeared on the market, cardiologists took patients off their β blockers and surgical patients had fits with hypertension and tachycardia during surgery. Now, finally, surgical patients are back on β blockers. I don't know that the withholding of β blockers resulted in increased myocardial damage, but we certainly saw more ischemia. I think maintaining patients on their β blockers is useful, and to have a drug like esmolol, where one can give the patient a short-lasting β-blocker, is even more useful.

Dr. Lowenthal (Philadelphia, Pennsylvania): How much of a pressor response is there during intubation?

Dr. Reves: Well, it depends on the underlying anesthetic, ventricular function and a whole host of things. For example, in our patients, mean blood pressures rose to 130 mm Hg in the control group and were only about 110 in the esmolol group. However, that is because our patients were lightly anesthetized. If one looks at patients on high-dose opioids for intubation, you'll see that one can usually block a lot of that hypertension. You may see blood pressure increases to about a mean of around 90, and it's often transient.

Dr. Lowenthal: Do you think that the hypertension that Dr. Gray reported in coronary artery bypass graft patients might in part be related to prolonged intubation during and after surgery?

Dr. Reves: The answer to that is no. However, I know that there are responders and nonresponders and the patients who respond to intubation with high blood pressure levels are frequently those who will, when they begin to emerge from their anesthesia in the intensive care unit, have more problems with postoperative hypertension. We did a study looking at catecholamine levels several years ago, and we found that responders are those who really pour out a lot of norepinephrine. Clearly there is one group that does and one that does not respond to intubation with hypertension.

Dr. Morganroth (Philadelphia, Pennsylvania): How often did you see esmolol-induced hypotension, and in your personal experience, how do you treat it in a given setting?

Dr. Reves: The blood pressure went down, but not to very low levels. We had 1 patient who went to less than 90 mm Hg, so we turned off the esmolol and gave a little phenylephrine. In most of our experience, blood pressure hasn't really dropped too low. To treat it, I would discontinue the drug. Most perioperative hypotension is due to vasodilation caused by the induction of anesthesia, and we end up giving volume and phenylephrine.

Dr. Lee (McGaw Park, Illinois): I would like you to comment on the clinical significance of perioperative tachycardia and hypertension, and where you see esmolol fitting in—both in coronary artery bypass graft patients and in patients with coronary disease going for noncardiac surgery. Just where do you see esmolol being used?

Dr. Reves: I see that esmolol is going to be on the anesthesiologist's cart, and it is primarily going to be used in patients in whom you are really worried about increases in heart rate—that is, patients with ischemic heart disease. There are others, but for the most part that's the primary group. Esmolol will be used to tide the patient through sinus tachycardia or serious hypertension, and you will just either hang esmolol as a drip or you may even squirt it in. Because esmolol is so short-lived, you can get better and faster control of the situation—and then may deepen your anesthesia or whatever other manipulations you have to do. That is the beauty of esmolol, and I think it will be used a great deal by clinicians, particularly those accustomed to giving vasoactive drugs—principally anesthesiologists. I also think esmolol will be used quite frequently to control unwanted hypertension and tachycardia, particularly sinus tachycardia and problems during an operation. I don't think esmolol will be necessarily used to try to block the increase in heart rate for intubation in the healthy patient, because we know that that is well tolerated; we see it every day and it is not a serious problem. However, esmolol will be used in patients with ischemic heart disease undergoing cardiac and noncardiac surgery.

Dr. Lowenthal: Do you know whether there is any experience with the use of esmolol during pheochromocytoma surgery, and if so, is it better than propranolol?

Dr. Laddu (McGaw Park, Illinois): We do not have such experience in any of the patients we've studied; but we plan to study this area.

Dr. Lee: I would guess that such patients would be better controlled on esmolol.

Dr. Reves: Yes, that would obviously be a good place to use esmolol.

Dr. Gray (Los Angeles, California): I would like to add to Dr. Reves' earlier comments. As I see it, there are serious problems with using esmolol only in patients with supraventricular tachycardia. Hypotension may be a limitation and esmolol will have competition in the marketplace. Verapamil is pretty good for supraventricular tachycardia, as is propranolol and digoxin. But in the patient with hypertension—whether it is postoperative, a patient who walks in with a hypertensive crisis or the occasional postinfarction patient who has a hyperdynamic circulation—I think that's

a situation where you can almost be assured that you can give esmolol in very large doses and with great safety, based on everything I've seen today. Of course, there may be other factors that we haven't seen yet. The number of patients who may benefit from this drug is substantial. Just looking at the coronary bypass surgery market, if you will, the estimate in 1983 was that there were 190,000 coronary bypass surgeries performed. That's probably down a little in 1984, and maybe it will go further down in 1985. Let's say 150,000 patients have bypass surgery in 1985, of whom anywhere from 25 to 60% are hypertensive and, say, half of those would qualify for esmolol or some β blocker. I think we are looking at a sizable number of patients for which esmolol would be very good therapy.

Dr. Reves: I think it will be an adjunct to nitroprusside, too, in postoperative hypertension. At the moment, we think of drugs as appropriate for different patient groups, but I would be willing to bet that ultimately esmolol will be used right alongside nitroprusside in many of those postoperative hypotensive patients.

Dr. Morganroth: I could make the same comment about the verapamil issue, too. I would think one could argue that esmolol should be the first-line agent instead of verapamil, for the reasons we talked about before.

Dr. Reves: Yes, and verapamil causes profound hypotension. Every time I give verapamil, I'm just a little apprehensive because I know the blood pressure is going to go so low.

NOVEMBER 1, 1985

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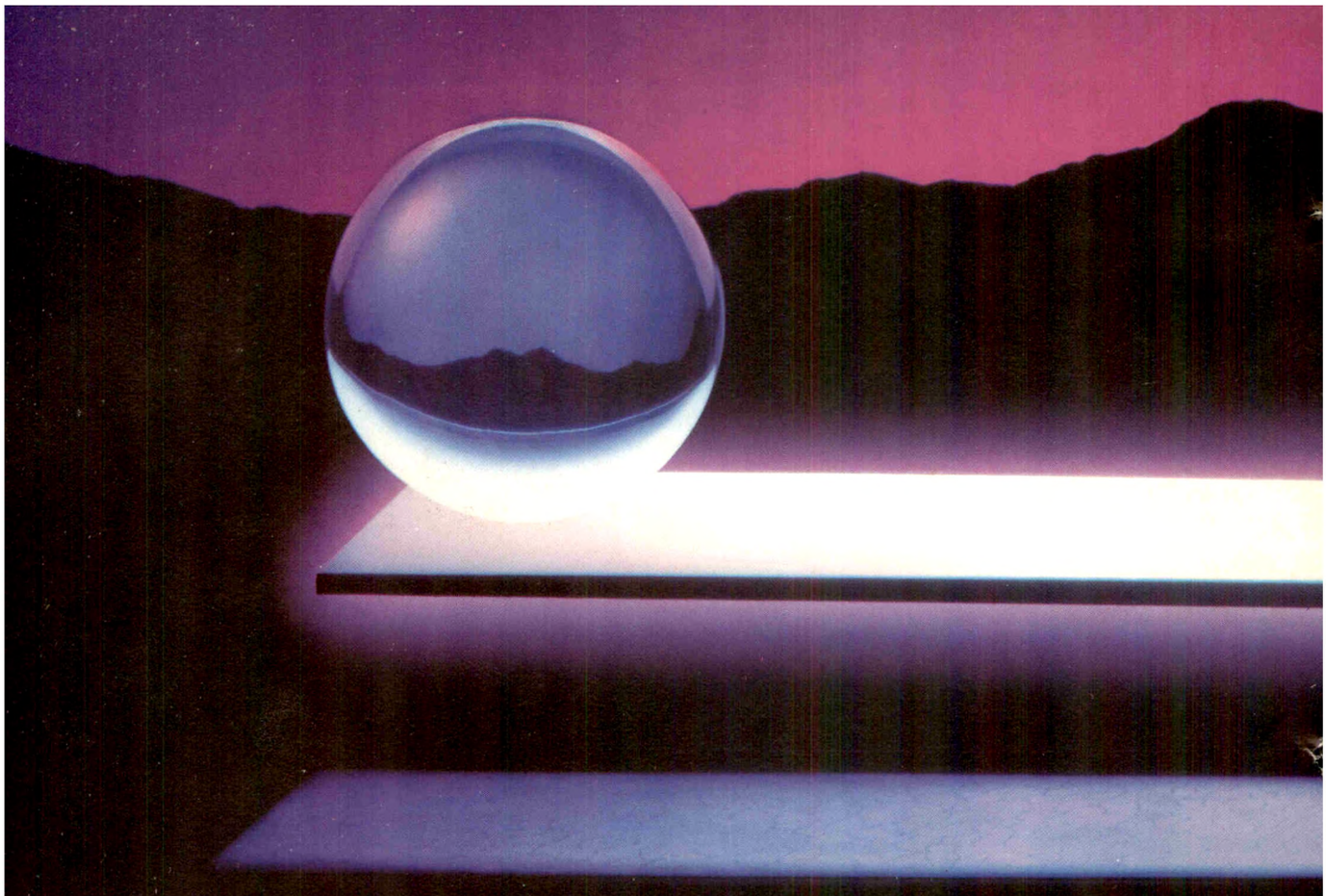

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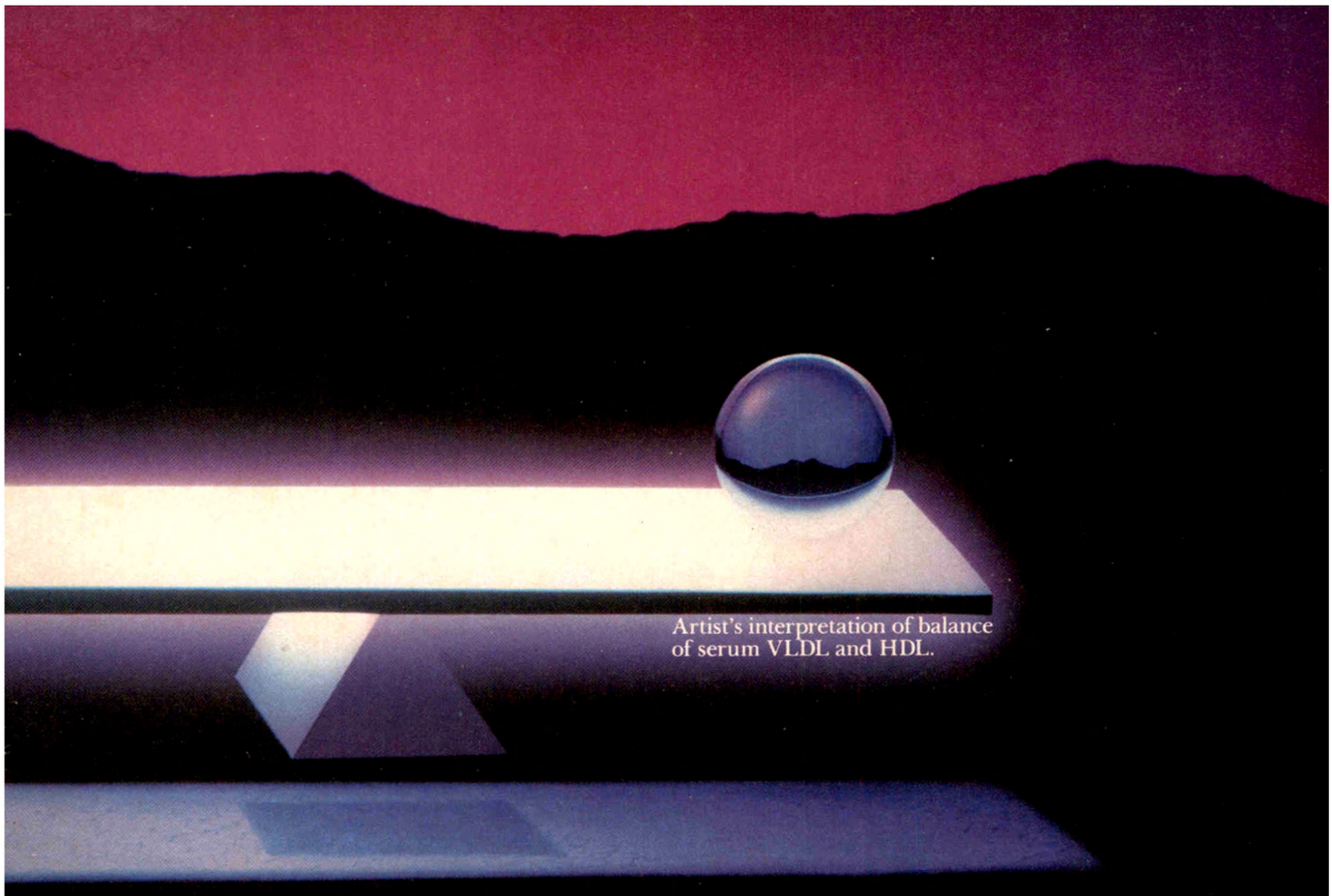
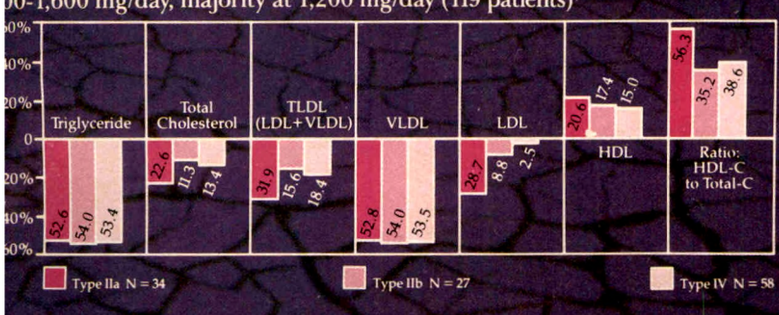


Artist's interpretation of balance of serum VLDL and HDL.

to Therapy of Certain Dyslipidemias

Lipid-regulating efficacy: open-label phase of US multicenter study at end of 12 lunar months*[1]

Average percent change from baseline at doses ranging from 800-1,600 mg/day, majority at 1,200 mg/day (119 patients)†



Diet, exercise and weight loss are the first choice in therapy of lipid disorders.

*Visit every 4 weeks during long-term use of LOPID.

†Data cited on this graph reflect clinical experience based on the multicenter trial. They do not imply an indication for Types IIa and IIb dyslipidemias.

1. Data on file, Medical Affairs Dept, Parke-Davis.

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Please see following page for brief summary of prescribing information.

TWO-WAY LIPID REGULATOR

LOPID®

(gemfibrozil capsules, USP) 300 mg

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO
		Total	VLDL	LDL	HDL	HDL Cholesterol / Total Cholesterol
IIa	−44%	−4.2%	−44.3%	− 5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	− 6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil capsules, USP) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (see WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings.)

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil capsules, USP) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria
Central Nervous System: headache, dizziness, blurred vision
Musculoskeletal: painful extremities
Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:
Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia
Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints
Central Nervous System: vertigo, insomnia, paresthesia, tinnitus
Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)
Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL CAPSULES, USP). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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BRIEF SUMMARY

INDICATIONS—Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency of, or eliminate, anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack. Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.
PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.
ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.
DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25, 50 and 75 mg. For complete details, please see the full prescribing information.

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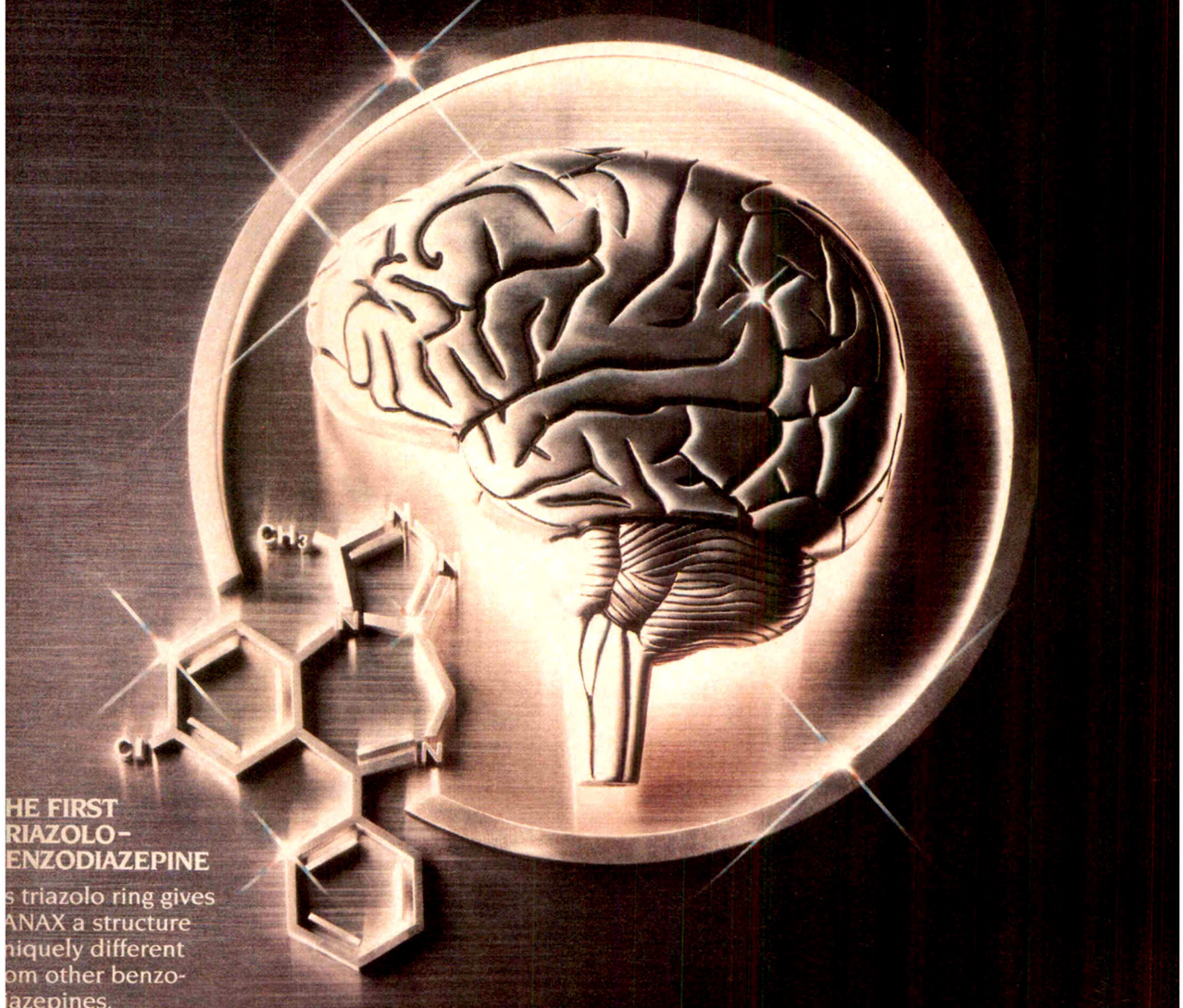

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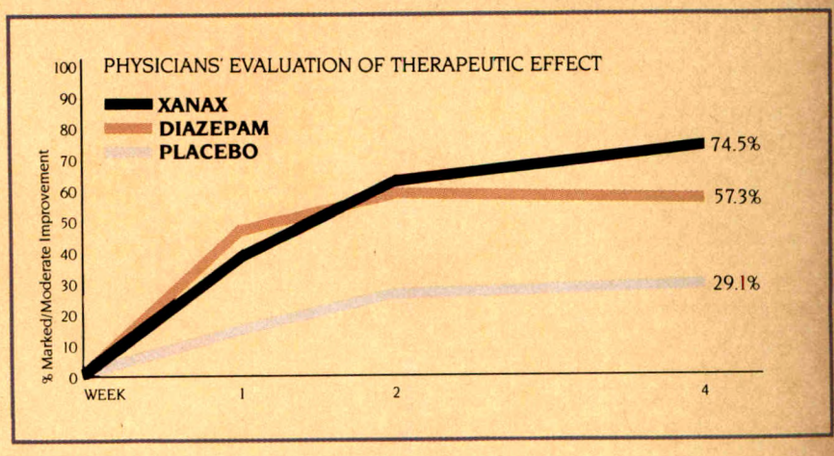

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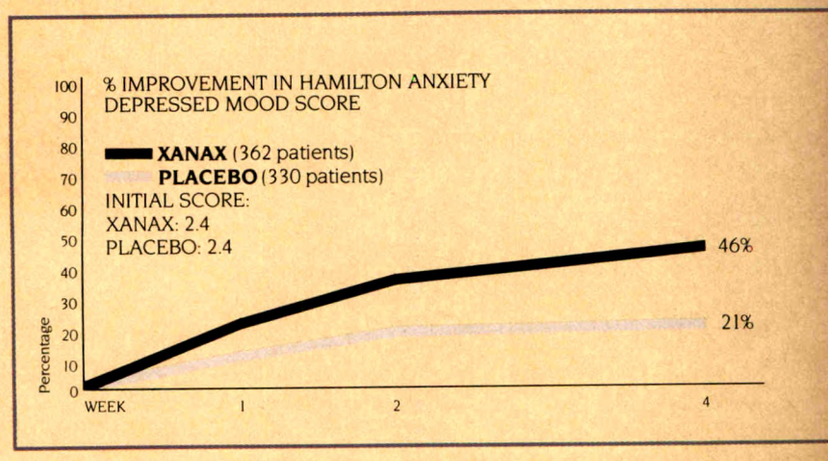

SIMPLE DOSAGE:
XANAX 0.25–0.5 mg T.I.D.

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CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-3-S

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. J Clin Psychiatry 42 (9):347-351, 1981.

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INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria – Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C – There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets.
(J3-658C)

Reference: 1. Cannon PJ, Criley JM, Dzau VJ, et al: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Col Cardiol 2:755–763, 1983.

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INNOVATORS IN CARDIOVASCULAR MEDICINE

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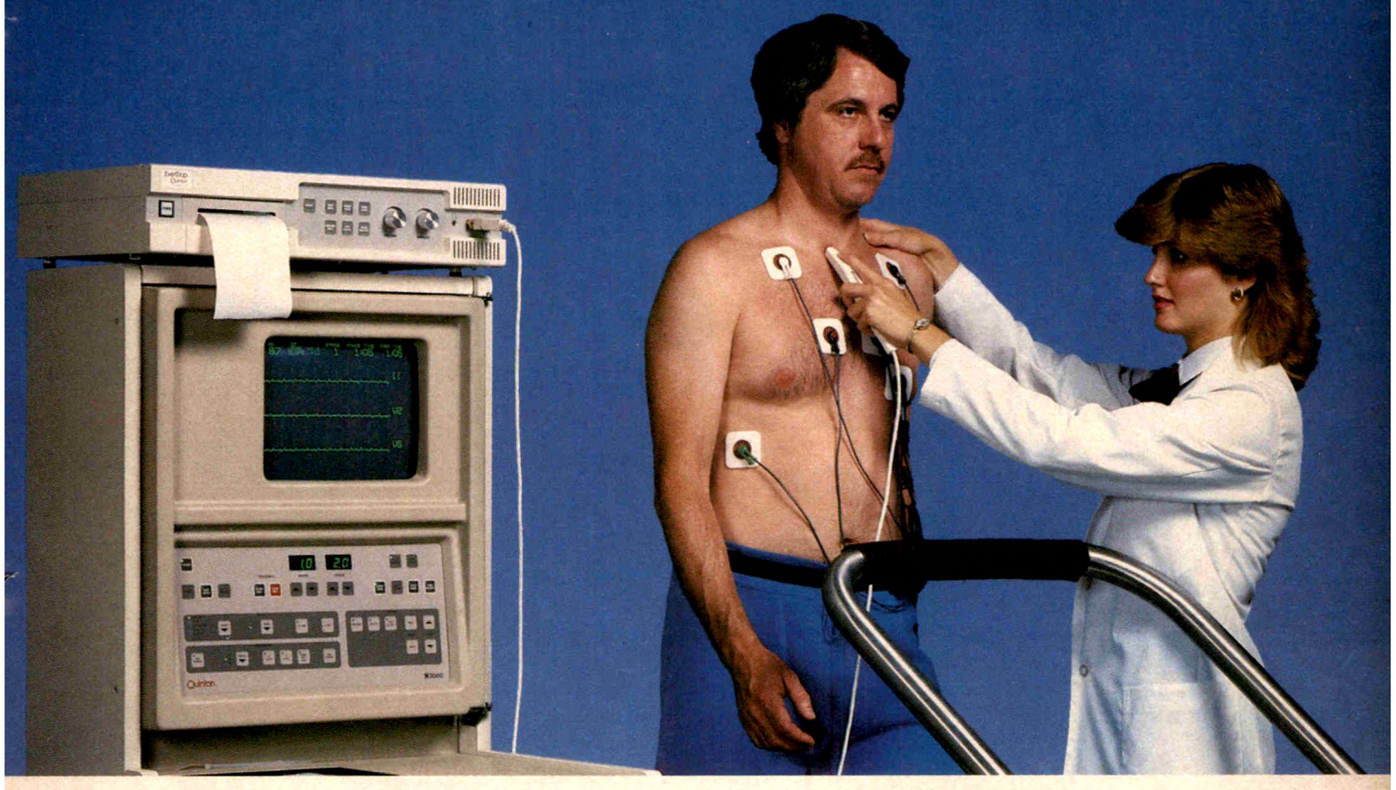
Introducing a Noninvasive Method for Assessing Left Ventricular Function



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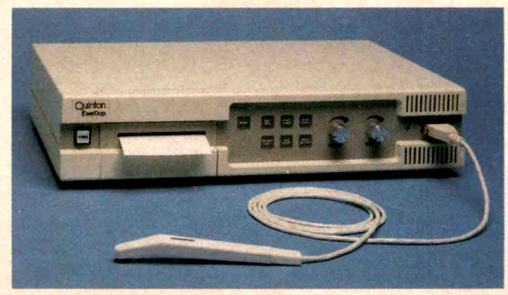

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Quinton will be exhibiting ExerDop at the AHA 58th Scientific Sessions. Stop by booth 4224 for a demonstration.

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705 Effect of Intracoronary Thrombolytic Therapy on Exercise-Induced Ischemia After Acute Myocardial Infarction

JACQUES A. MELIN, PATRICK M. De COSTER, JEAN RENKIN, JEAN-MARIE R. DETRY, CHRISTIAN BECKERS, and JACQUES COL

Thirty-nine patients enrolled in an angiographically randomized trial of intracoronary streptokinase (SK patients treated with SK; 20 control subjects) underwent thallium-201 scintigraphy at rest and during stress 5 weeks after acute myocardial infarction. The patients were classified into 2 groups based on the presence 13) or absence (n = 26) of complete obstruction of the infarct-related coronary artery at the end of the acut giographic procedure. Semiquantitative score of myocardial thallium uptake was expressed as perce maximal defect score. Thallium defect score at rest between admission and 5 to 6 weeks' study decreased 10 ± 16% units in the control group and from 23 ± 14% units in the SK group (p = 0.01). This decrease wa lated to opening of the infarct-related artery (opening 23 ± 16% vs occlusion 5 ± 10%). The change in the cise-induced defect score was significantly (p = 0.01) larger in patients in the SK group (11 ± 6% units) th those in the control group (5 ± 7% units). The exercise perfusion defect was larger (p = 0.006) in patients incomplete obstruction or reperfusion (10 ± 6% units) than in patients with complete obstruction (3 ± 7% u This difference was independent of the number of diseased coronary vessels. Thus, in this group of patients were studied 5 to 6 weeks after acute myocardial infarction, patients treated with SK showed scintigra improvement at rest compared with results on admission, but had more exercise-induced ischemia; this related to incomplete coronary obstruction or reperfusion.

712 Primary Angiographic Success Rates of Percutaneous Transluminal Coronary Angioplasty

H. VERNON ANDERSON, GARY S. ROUBIN, PIERRE P. LEIMGRUBER, JOHN S. DOUGLAS, Jr., SPENCER B. KING III, and ANDREAS R. GRUENTZIG

Since the advent of coronary angioplasty, 3 distinct periods in catheter design can be identified. Double-lu balloon catheters with a fixed, flexible guidewire were first used. These were replaced with indepen steerable guidewires and catheters. Finally, the low-profile catheter was introduced. We separated our ex ence in 2,969 patients undergoing single-vessel percutaneous transluminal coronary angioplasty of a n coronary artery into 3 periods corresponding to the use of the 3 distinct catheter types. Before introducti steerable and low-profile catheters there was a significant difference among the 3 major coronary arteries i ability to reach and cross stenoses. This difference no longer exists. The percentage of total percutan transluminal coronary angioplasty attempts in the left anterior descending artery has decreased, whereas i left circumflex and right coronary arteries it has increased. Stenoses in all 3 major coronary arteries are equally accessible and primary success rates are similar.

718 Digital Quantification Eliminates Intraobserver and Interobserver Variability in the Evaluation of Coronary Artery Stenosis

RAN VAS, NEAL EIGLER, CALVIN MIYAZONO, J. MARTIN PFAFF, KENNETH J. RESSER, MASON WEISS, THASANA NIVATPUMIN, JAMES WHITING, and JAMES FORRESTER

Four experienced angiographers independently determined percent diameter narrowing of 36 stenoses us methods: by subjective analysis of single-frame cine film images (film); by subjective analysis of digital nonenhanced single-frame images (digital); and by using a semiautomated digital caliper quantitation sy

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Tablets

BRIEF SUMMARY

INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS

Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

PRECAUTIONS

General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600
Number of Patients	522	181	606	608
Dizziness (%)	2	3	3	3
Fatigue	2	1	4	4
Nausea	<1	0	1	2
Vomiting	0	0	<1	<1
Dyspepsia	1	0	2	1
Paresthesias	2	0	2	2
Nasal Stuffiness	1	1	2	2
Ejaculation Failure	0	2	1	2
Impotence	1	1	1	1
Edema	1	0	1	1

Labetalol HCl Daily Dose (mg)	800	900	1200	1600	2400
Number of Patients	503	117	411	242	175
Dizziness (%)	5	1	9	13	16
Fatigue	5	3	7	6	10
Nausea	4	0	7	11	19
Vomiting	<1	0	1	2	3
Dyspepsia	1	0	2	2	4
Paresthesias	1	1	2	5	5
Nasal Stuffiness	2	2	4	5	6
Ejaculation Failure	3	0	4	3	5
Impotence	2	4	3	4	3
Edema	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes Dry eyes.

Immunological System Antimitochondrial antibodies.

Liver and Biliary System Cholestasis with or without jaundice.

Musculo-Skeletal System Muscle cramps; toxic myopathy.

Respiratory System Bronchospasm.

Skin and Appendages Rashes of various types, such as generalized maculo-papular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block. See **CONTRAINDICATIONS**.

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a $beta_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered three times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED

NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

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NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).

NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.

For complete prescribing information, please consult package insert.

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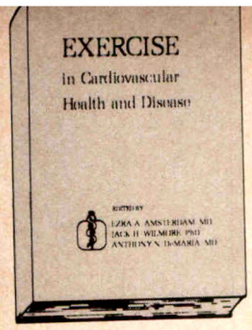

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Edited by
Ezra A. Amsterdam, MD, Chief Coronary Care Unit, Univ. of Calif. School of Medicine
Jack H. Wilmore, PhD, Professor and Head Dept. of Physical Education & Athletics, Univ. Arizona
Anthony N. DeMaria, MD, Dir. Echocardiography Section, Univ. of Calif. School of Medicine

SEPTEMBER 1977, 408 PAGES, ILLUS.

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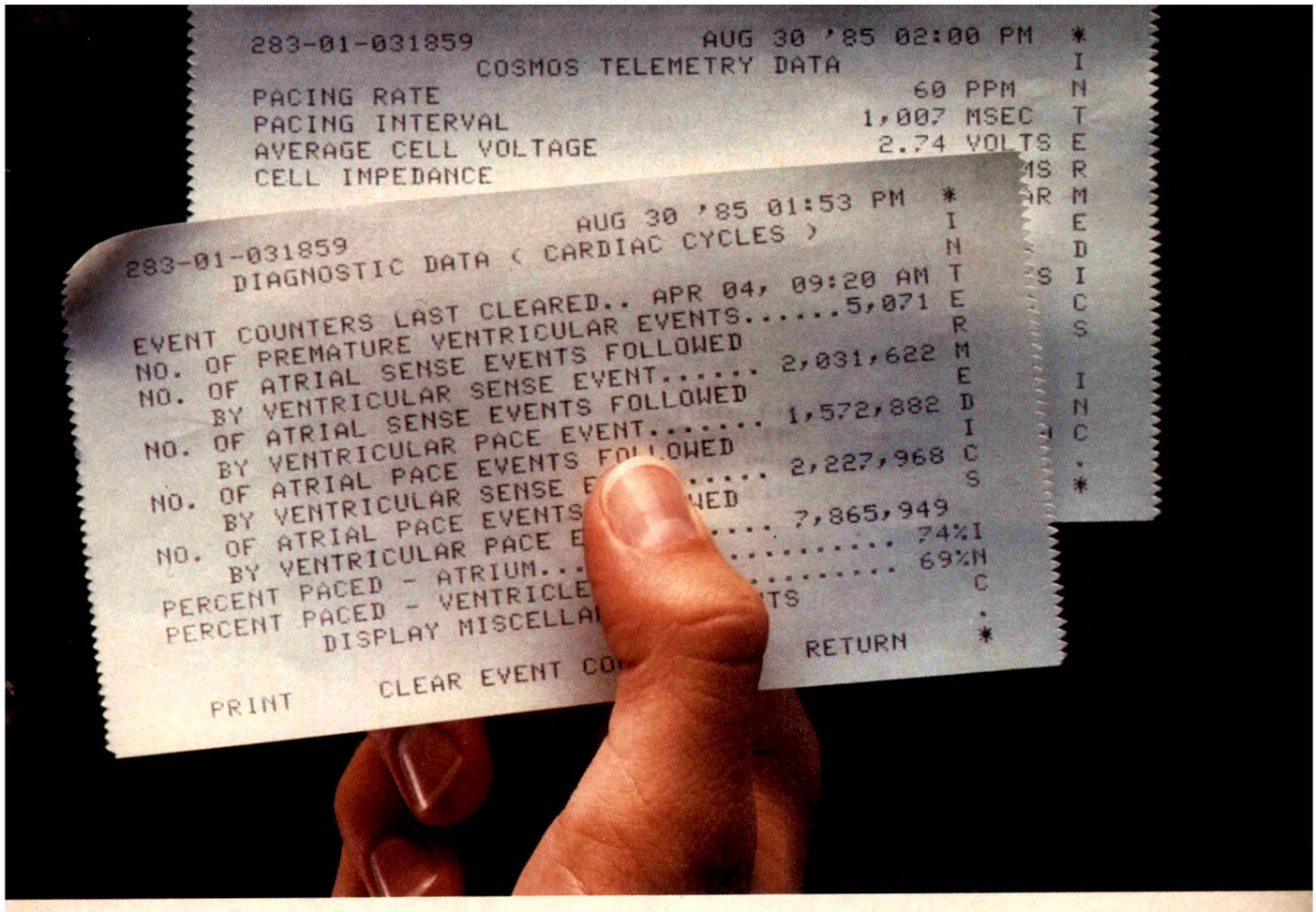

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(Corona). Digital and Corona readings correlated well with subjective interpretation of film ($r > 0.85$ for both). Corona markedly improved intraobserver ($p < 0.005$) and interobserver ($p < 0.001$) reproducibility. Corona less frequently misclassified individual observations than did film when categories of less than 50, 50 to 75 and more than 75% diameter stenosis were used (3.7% vs 31.5%, $p < 0.001$). Our results suggest that automatic measurement of coronary stenosis is accurate compared with measurements by a group of experienced angiographers, and for the practical purpose of clinical decision making, it eliminates intraobserver and interobserver variability.

724 Comparison of Buccal Nitroglycerin and Oral Isosorbide Dinitrate for Nitrate Tolerance in Stable Angina Pectoris

JOHN O. PARKER, KAREN A. VANKOUGHNETT, and BERNICE FARRELL

Sixteen patients with chronic, stable exertional angina pectoris were studied to compare the hemodynamic and antianginal effects of buccal nitroglycerin (GTN) and oral isosorbide dinitrate (ISDN). During acute therapy, both buccal GTN (3 mg) and oral ISDN (30 mg) decreased systolic blood pressure at rest for 5 hours. During sustained 3-times-daily therapy with buccal GTN and 4-times-daily therapy with oral ISDN, no significant changes were seen in systolic blood pressure at rest. Treadmill walking time increased significantly over the 5-hour period during acute and sustained administration of buccal GTN. The acute response to oral ISDN was similar to that with buccal GTN, but during sustained therapy with ISDN the improvement in treadmill walking time was diminished and persisted for only 1 hour. This investigation suggests that nitrate tolerance develops with 4-times-daily therapy with oral ISDN but not during 3-times-daily therapy with buccal GTN.

729 Collateral Flow in Patients with Acute Myocardial Infarction

WILLIAM D. NITZBERG, HRUDAYA P. NATH, WILLIAM J. ROGERS, WILLIAM P. HOOD, Jr., PATRICK L. WHITLOW, RUSSELL REEVES, and WILLIAM A. BAXLEY

Using a system developed to assess collaterals in a semiquantitative fashion from coronary arteriograms, infarct-zone collaterals were examined at the time of and 2 weeks after acute myocardial infarction in 53 patients undergoing emergency angiography and reperfusion interventions. Baseline collaterals were sparse; collaterals were more extensive 2 weeks after acute myocardial infarction, and they increased primarily in patients with occluded infarct-related arteries at follow-up angiography. Improvement in global ejection fraction at repeat angiography among patients with occluded infarct-related vessels during acute myocardial infarction tended to be associated with higher baseline collaterals scores.

737 Frequency and Significance of Induced Sustained Ventricular Tachycardia or Fibrillation Two Weeks After Acute Myocardial Infarction

ANIL K. BHANDARI, JEFFREY S. ROSE, ADAM KOTLEWSKI, SHAHBUDIN H. RAHIMTOOLA, and DELON WU

Electrophysiologic stimulation studies, 24-hour ambulatory electrocardiographic monitoring and angiographic evaluations were prospectively performed in 45 patients 9 to 21 days after acute transmural myocardial infarction. Of 45 patients, 20 (44%) had induction of sustained ventricular tachycardia or fibrillation (group I). These patients had more severe wall motion abnormalities and a higher incidence of left ventricular aneurysms than the 25 patients with no inducible sustained ventricular tachyarrhythmias (group II). During a mean follow-up of 10 ± 3 months, 1 patient in each group died suddenly and 1 patient in group I had spontaneous sustained ventricular tachycardia. Electrical induction of sustained ventricular arrhythmias is common 2 weeks after acute infarction, but appears to be of limited prognostic significance.

742 Crossover from Intravenous to Transdermal Nitroglycerin Therapy in Unstable Angina Pectoris

SHU-GUANG LIN and JOHN T. FLAHERTY

The present study was designed to examine the safety and efficacy of titrating intravenous (i.v.) nitroglycerin to a fixed hemodynamic endpoint as the initial therapy for patients admitted to a coronary care unit for medically refractory unstable angina, and to test the hypothesis that patients, responding to the addition of i.v. nitroglycerin

Continued on page A24

dications: Quinidex Extentabs are dicated in the treatment of: premature rial and ventricular contractions, roxysmal atrial tachycardia, paroxmal A-V junctional rhythm, atrial flut-, paroxysmal atrial fibrillation, tablished atrial fibrillation when erapy is appropriate, paroxysmal ventcular tachycardia when not associated th complete heartblock, maintenance erapy after electrical conversion of rial fibrillation and/or flutter.

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recautions: All the precautions apply g to regular quinidine therapy apply to is product. Use with care in patients th severe congestive failure, renal inefficiency or with digitalis intoxication. Patients should be carefully observed r sign of toxicity: e.g., (1) allergy or osyncrasy, such as febrile reactions, in eruptions, and thrombocytopenia xtremely rare); (2) "cinchonism," such tinnitus, blurred vision, dizziness, htheadedness, and tremor; (3) G-I mptoms (nausea, vomiting, diarrhea, d colic); (4) cardiotoxic effects such as ntricular extrasystoles occurring at a e of one or more every 6 normal beats, increase of the QRS complex of 50% more, a complete A-V block, or ventcular tachycardia.

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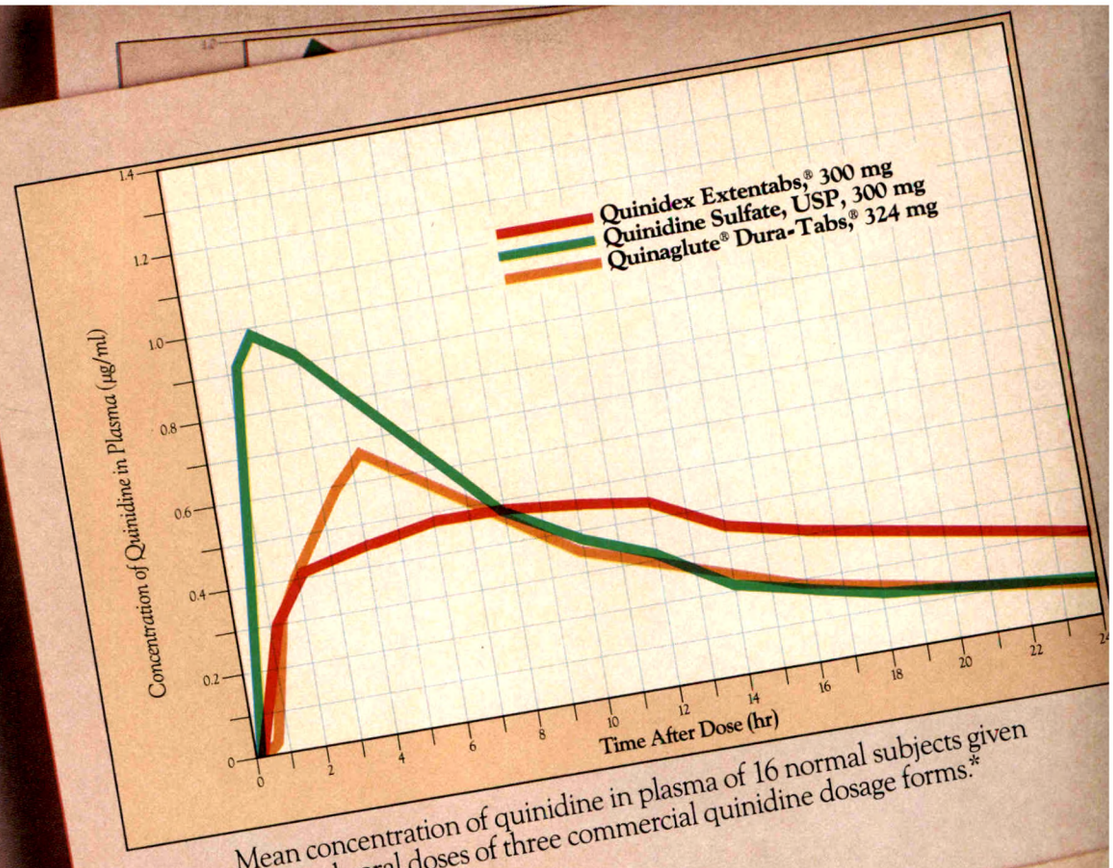

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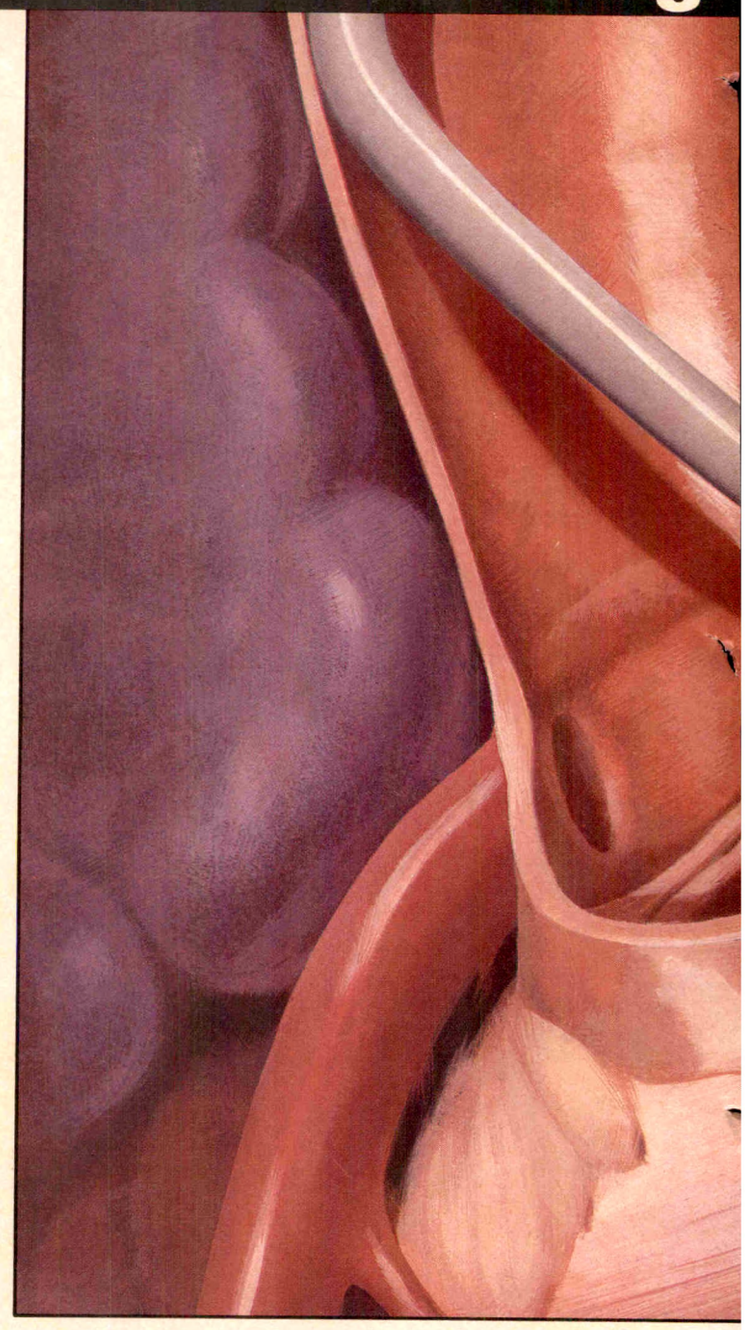

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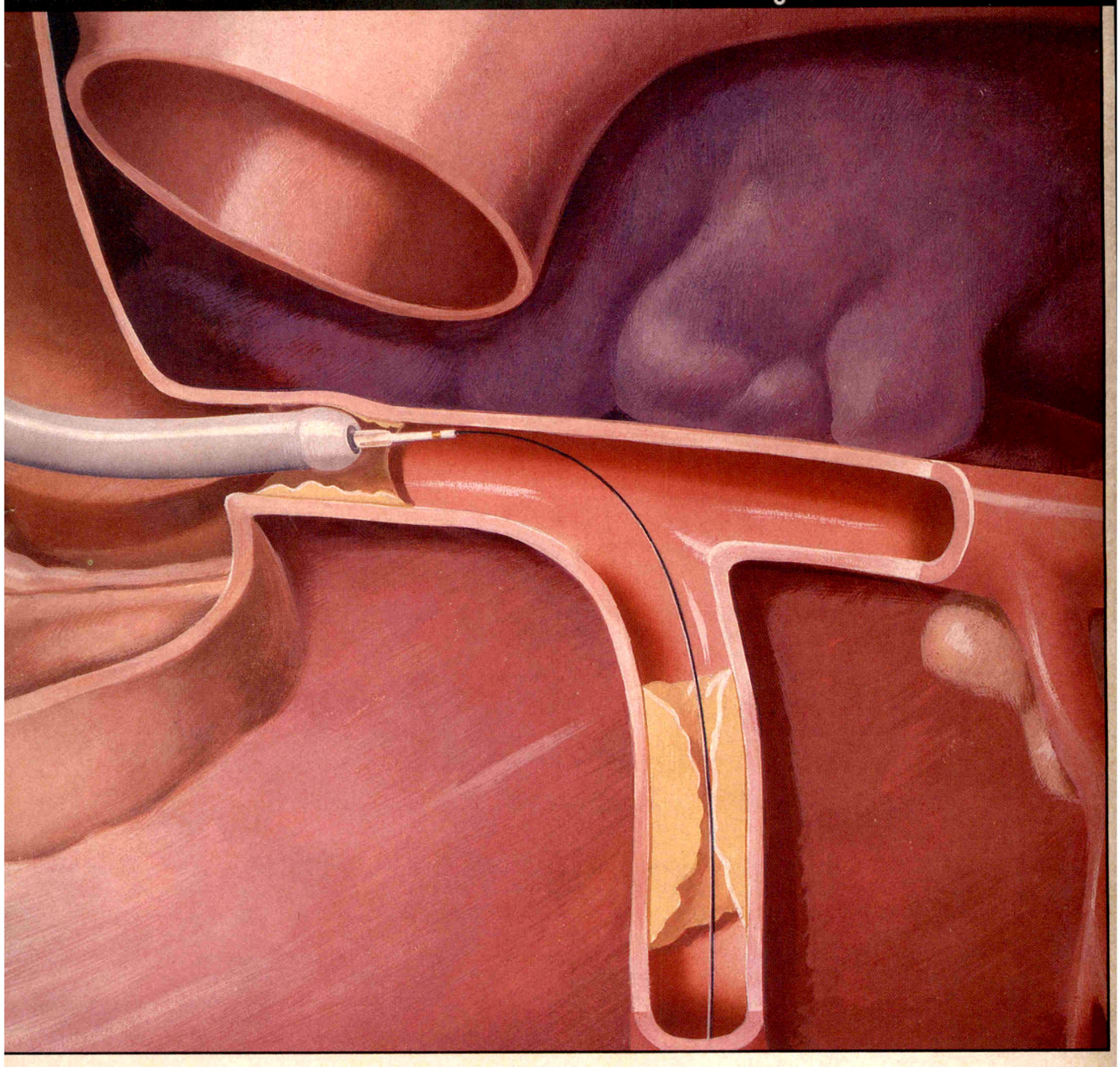

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to their previous antianginal regimen, could be crossed over to nitroglycerin administered by one of the new transdermal delivery systems. Nine patients had a nitroglycerin infusion titrated to a 10% reduction in mean arterial pressure, which resulted in cessation of episodes of chest pain at rest in all 9. Subsequently, this treatment strategy was tested in 17 consecutive patients treated in our coronary care unit during a 1-month period for unstable angina. Ten of 15 successfully treated patients had an ischemia as the cause of their chest pain documented by cardiac catheterization and no change in antianginal or vasoactive drugs during crossover to transdermal therapy. In 4.8 ± 0.9 hours, all 10 patients were tapered off i.v. nitroglycerin (84 ± 74 μg/min, range 10 to 200) and crossed over in a stepwise fashion to transdermal nitroglycerin patches (22.5 ± 10 mg/24 hours, range 5 to 40), while maintaining the mean arterial pressure reduction achieved with i.v. therapy. Among these 10 patients, 7 had no further pain episodes throughout the remainder of their hospitalization. Two patients had a single episode of chest pain, after transient interruption of transdermal nitroglycerin therapy in 1 and transient reduction of the transdermal dose in the other. These results suggest that i.v. nitroglycerin is safe and effective treatment for patients with unstable angina admitted to a coronary care unit, and that the new transdermal nitroglycerin delivery systems successfully maintain these beneficial effects.

749 Ischemia During Angioplasty After Streptokinase: A Marker of Myocardial Salvage

LOWELL F. SATLER, CHARLES E. RACKLEY, CURTIS E. GREEN, RANDOLPH S. PALLAS, DAVID L. PEARLE, ALBERT A. DEL NEGRO, and KENNETH M. KENT

Thrombolytic therapy in acute myocardial infarction has not clearly demonstrated myocardial salvage as assessed by enzymatic, electrocardiographic, or regional wall motion evaluation of the left ventricle. After successful reperfusion, however, patients frequently experience recurrent episodes of chest pain, presumably owing to transient reocclusion of the infarct vessel. To recognize salvaged myocardium, the effects of coronary angioplasty soon after thrombolytic therapy were reviewed. Controlled reocclusion of the infarct vessel with a balloon catheter resulted in electrocardiographic or ischemic changes in 21 of 55 patients. These ischemic changes suggest the presence of persistently viable, salvaged myocardium in the distribution of the reperfused infarct vessel.

753 Evaluation of Methods of Measurement and Estimation of Left Ventricular Function After Acute Myocardial Infarction

MICHAEL G. JONES, BARRY W. RAMO, GILBERT L. RAFF, TOMOAKI HINOHARA, and GALEN S. WAGNER

Multiple gated blood pool imaging and single-plane contrast ventriculography were used to obtain 2 independent measures of left ventricular (LV) ejection fraction (EF) in each of 21 patients seen 2 to 6 weeks after their first acute myocardial infarction (AMI). These measures were then compared with the extent of myocardial necrosis estimated from a standard 12-lead electrocardiogram using the complete Selvester QRS scoring system. Correlation coefficients between the 2 measures of LVEF were similar to those previously reported for non-AMI populations. A QRS score of 4 or less achieved 100% specificity and a score of 8 or less, 100% sensitivity for predicting an LVEF greater than 40%. Thus, the Selvester QRS scoring system may be of value in identifying patients with or without markedly impaired LVEF. This risk stratification may be important in reaching optimal post-AMI therapeutic decisions.

757 Infections in a Coronary Care Unit

WINSTON A. SCHANDORF, RICHARD B. BROWN, MICHAEL SANDS, and DAVID HOSMER

All infections within an active coronary care unit (CCU) were analyzed over a 3-year period to ascertain rates, outcomes, pathogens and infection sites. Two hundred thirty-six infections were documented in 200 patients. Infection rates were 5 and 2% for total and CCU-acquired infections, respectively. The latter accounted for 11% of nosocomial infections that occurred within all critical care areas surveyed. Lower respiratory and urinary tract infections were most commonly noted, with *E. coli*, *S. aureus* and klebsiella-enterobacter-serratia most usually implicated. Mortality among patients with infections was 31%, compared with 8 to 12% in those without infections. Patients with fewer respiratory infections or primary bacteremias had a higher mortality rate than

Continued on page A30

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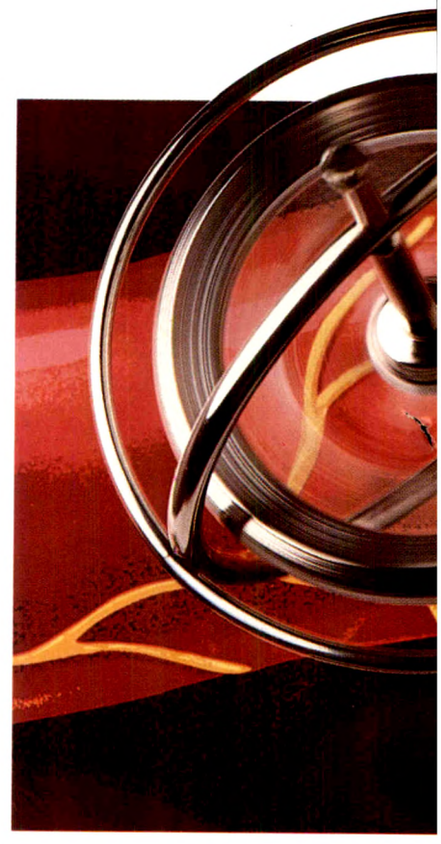

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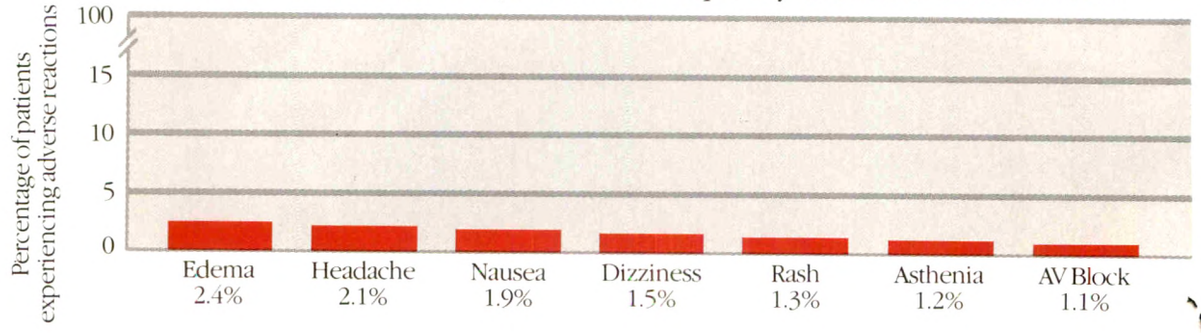
The adverse reactions reported most frequently with Cardizem have been:



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*Cardizem is indicated in the treatment of chronic stable angina (classic effort-associated angina) and angina due to coronary artery spasm.

Reduces angina attack frequency*

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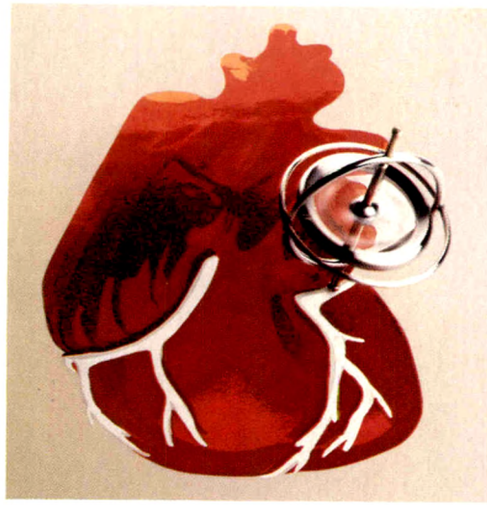

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- Decreases heart rate
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References:

1. Schroeder JS, Lamb IH, Ginsburg R, et al: Diltiazem for long-term therapy of coronary arterial spasm. *Am J Cardiol* 49:533-537, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78 (July suppl):234-238, 1980.
3. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. *Am J Cardiol* 49:560-566, 1982.

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BRIEF SUMMARY

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist).

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on an mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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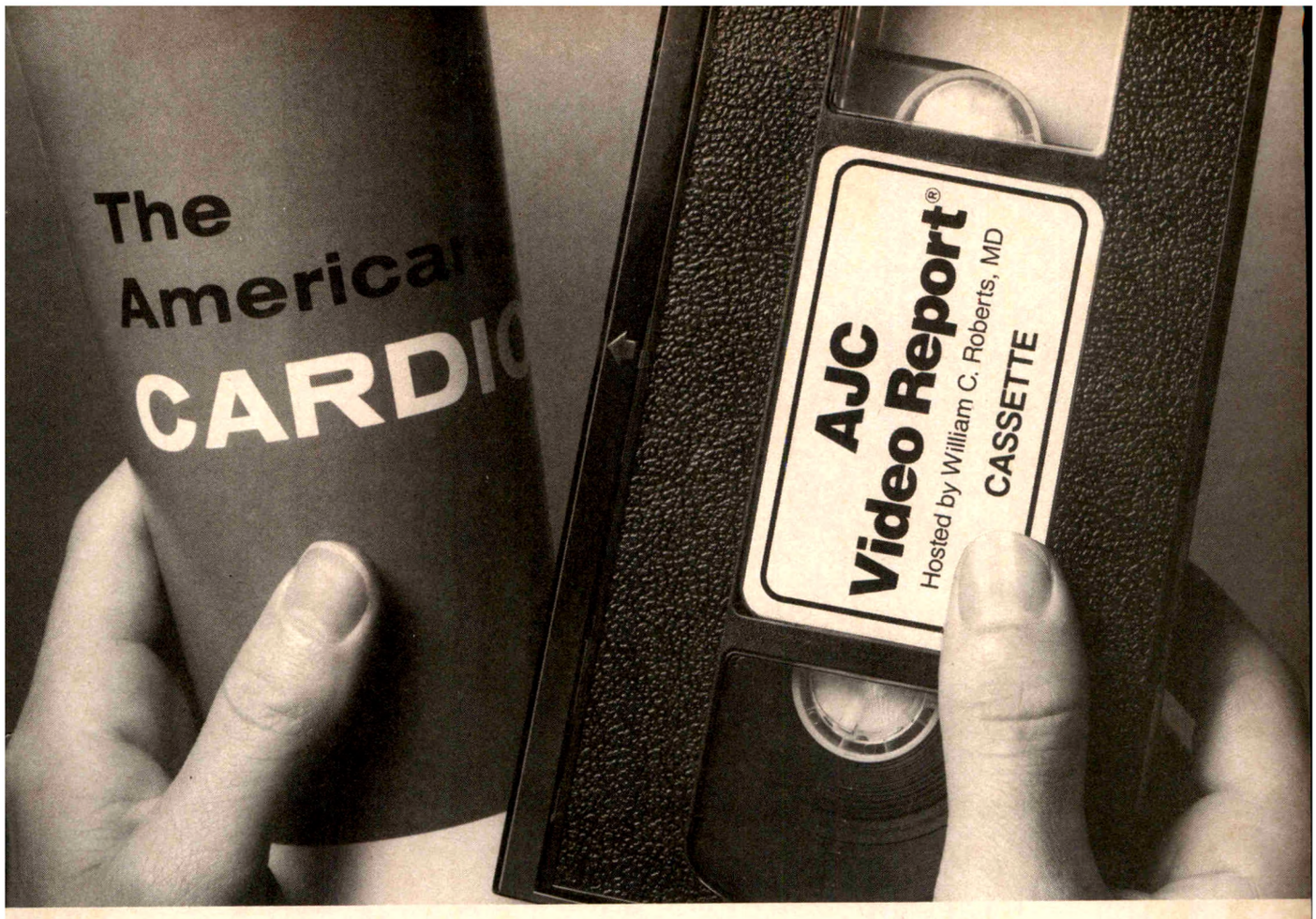

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persons infected at other sites ($p < 0.001$). Infections are seen in almost 5% of CCU patients. Mortality rates in infected patients may be 3 times higher than in the general CCU population. This study provides data against which other similar institutions can gauge their CCU infection rates

METHODS

761 Determination of Left Ventricular Mass Using Single-Photon Emission Computed Tomography

CHRISTOPHER L. WOLFE, DONALD E. JANSEN, JAMES R. CORBETT, KIRK LIPSCOMB, GREGORY GABLIANI, NEIL FILIPCHUK, GREGORY REDISH, SAMUEL E. LEWIS, and JAMES T. WILLERSON

This study tested the hypothesis that single-photon emission computed tomography (SPECT) accurately measures left ventricular (LV) mass in humans. SPECT measurements of LV mass were compared with LV mass determined by cineangiography in 12 patients. There was good correlation between LV mass determined by SPECT and by cineangiography ($r = 0.82$, root-mean-square deviation from regression = 24.7).

764 Analysis of Factors Affecting the Variability of Fick Versus Indicator Dilution Measurements of Cardiac Output

L. DAVID HILLIS, BRIAN G. FIRTH, and MICHAEL D. WINNIFORD

This study was performed to assess the relation between Fick and indicator dilution measurements of cardiac output (CO) in a large number of subjects, and to evaluate this relation in patients with a low CO, a high CO and left-sided regurgitation. In 808 patients, CO was measured by Fick and either thermodilution (right atrium to pulmonary artery) ($n = 252$) or indocyanine green dye (pulmonary artery to systemic artery) ($n = 556$). There was good agreement between Fick and both indicator dilution techniques. The disparity between Fick and indicator dilution was increased in patients with a low CO (less than 2 liters/min/m^2) ($n = 152$) and aortic or mitral regurgitation ($n = 83$). In these groups, the disparity between Fick and thermodilution was not increased, but the disparity between Fick and dye was exaggerated. Thus, thermodilution is preferable to indocyanine green dye in patients with a low CO or those with left-sided regurgitation.

769 Effect of Damped Sine-Wave Shocks on Catheter Dielectric Strength

GUST H. BARDY, FERNANDO COLTORTI, TOM D. IVEY, DAN YERKOVICH, and H. LEON GREENE

This study evaluated the ability of 24 new standard tripolar and quadripolar catheters to withstand a single damped sinusoidal shock delivered by a standard defibrillator. The schema for energy delivery was meant to simulate possible clinical practices. Delivered peak voltage and current were measured during each shock. Each electrode was examined for pitting and changes in line resistance as a consequence of the shock. Electrode pitting occurred on all selected anodal poles. However, it also was found on "unsolicited" electrodes from 7 catheters, indicating that current had followed unanticipated routes. Electrode line resistance was unmeasurable in 6 of these 7 inappropriately pitted electrodes. Delivered peak voltage and post-shock catheter dielectric strength depended on the manner of energy delivery. To simulate a posterior septal accessory pathway ablation procedure a shock was delivered to 2 proximal (anodal) poles in 16 quadripolar catheters (8 received 200 J and 8 received 360 J). Delivered peak voltage was 3,125 ± 362 V for the 200-J shock and 4,100 ± 160 V for the 360-J shock. Post-shock catheter dielectric strength for the 200- and 360-J shock was 1,425 ± 826 V and 601 ± 707 V, respectively. This was significantly lower than peak delivered voltage ($p < 0.001$ for either energy). To simulate His bundle or VT focus ablation, 8 tripolar catheters each received a single 200-J shock to the tip electrode. This resulted in a delivered peak voltage of 2,900 ± 351 V, compared with a post-shock dielectric strength of 1,325 ± 1,320 V ($p < 0.002$). Thus, standard catheters cannot control current flow adequately during a single high-energy shock because of inadequate dielectric strength. After the first shock an already inadequate dielectric strength deteriorates and increases the likelihood of current leakage with each subsequent shock.

Continued on page A35

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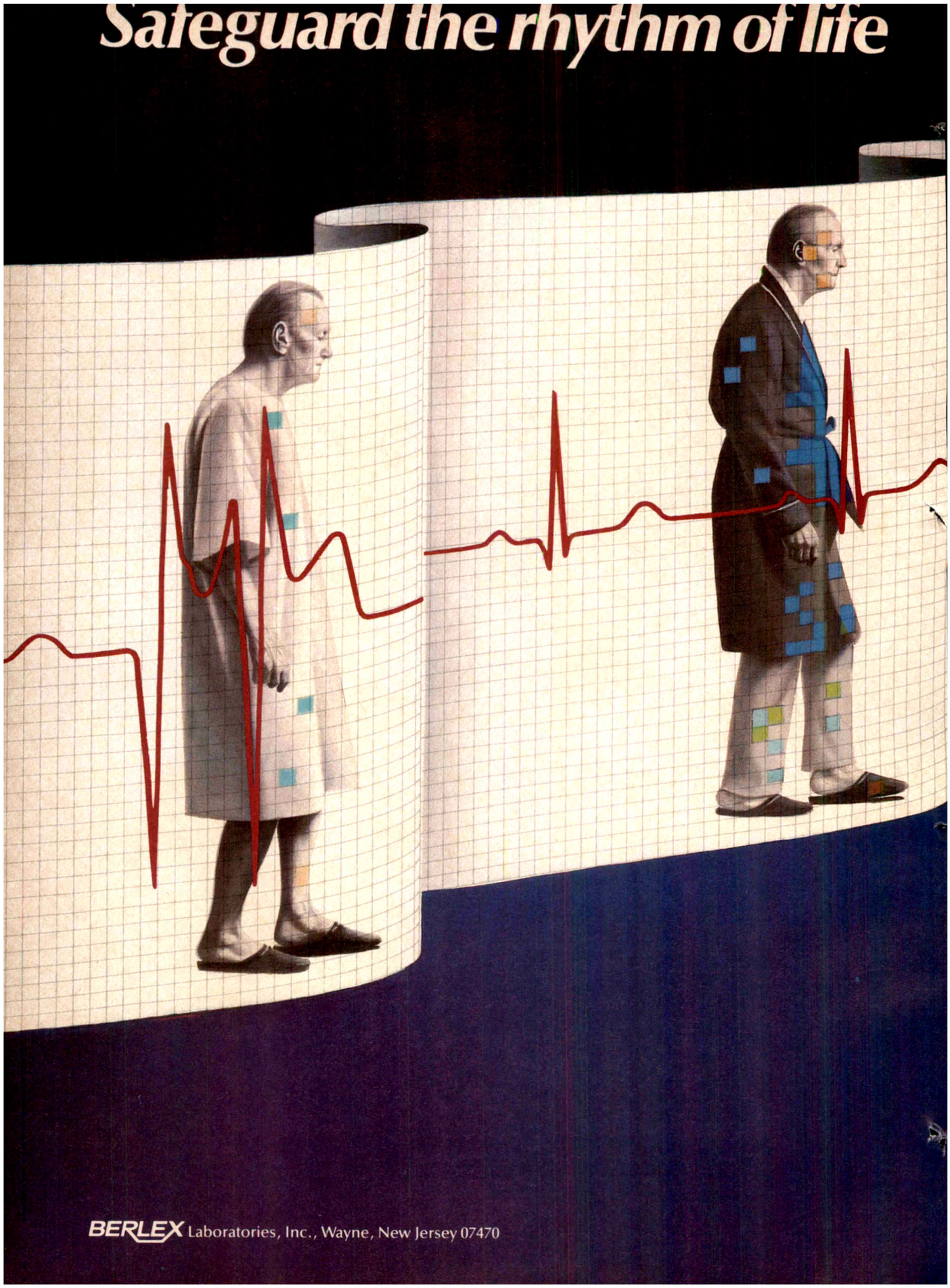

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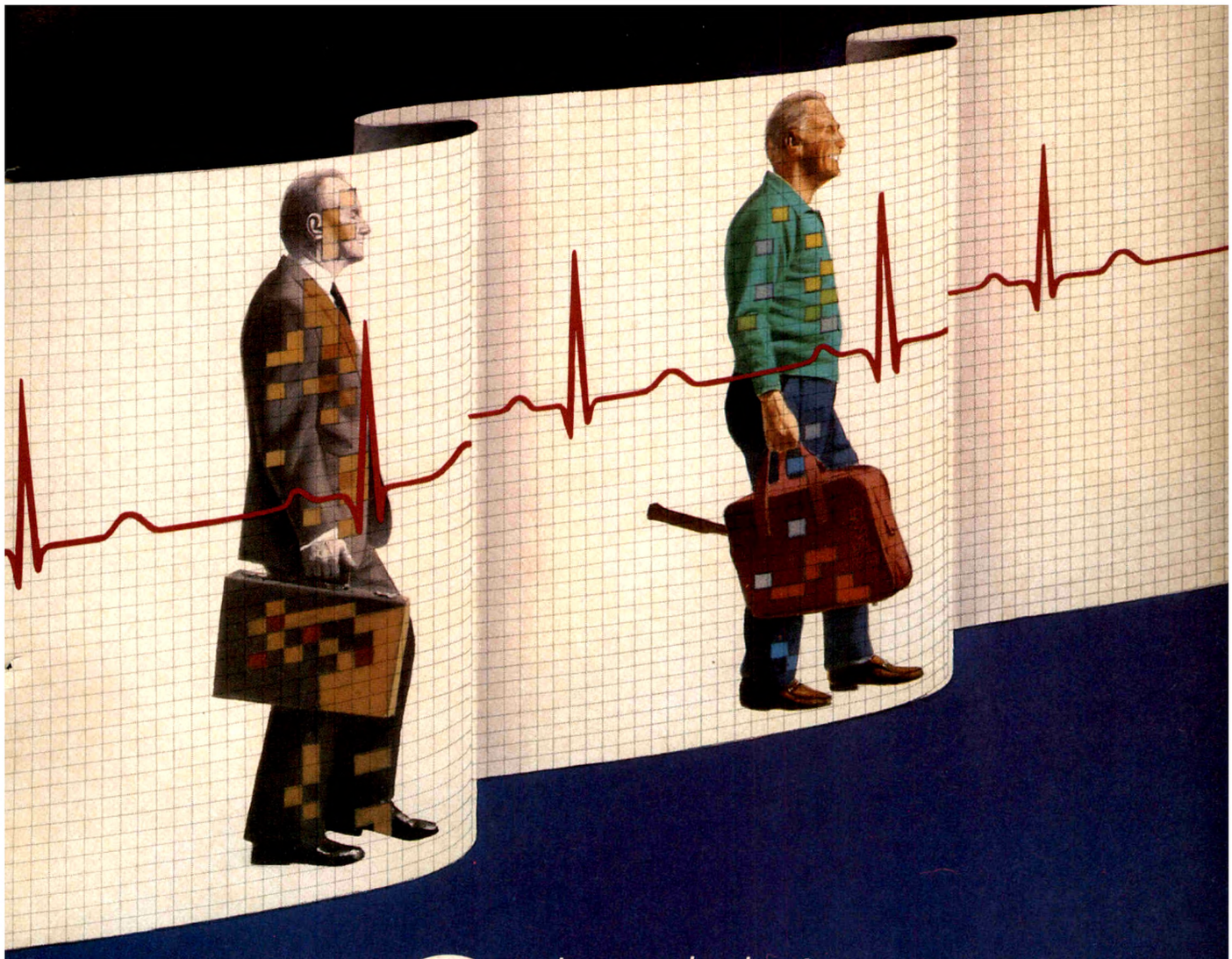

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References: 1. Selzer A: *Heart Lung* 1982;11:20-23.
2. Podrid P: *Patient Care* 1981;15:100-132.

INDICATIONS AND USAGE: Quinaglute (quinidine gluconate) Dura-Tabs are indicated in the prevention and/or treatment of:
1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).
2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).
CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine. 2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered. 3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring. 4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals. 5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity. 7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal. 8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk. *Information for Patients:* As with all solid oral medications, Quinaglute (quinidine gluconate) Dura-Tabs (sustained-release tablets) should be taken with an adequate amount of fluid, preferably in an upright position, to facilitate swallowing.

Drug Interactions: *Drug*	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea. Less frequently encountered adverse reactions:
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.
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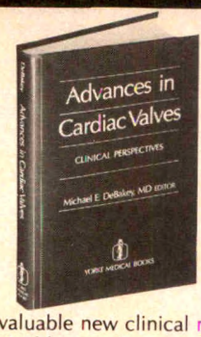

Advances in Cardiac Valves
Clinical Perspectives

edited by
Michael E. DeBakey, MD
0-914316-40-0, 1983, 274pp., $35.00

This valuable new clinical reference provides a detailed update on many aspects of mechanical heart valve prostheses, including hemodynamics, clinical results, results in children, non-invasive assessments, special indications, and implant techniques. Each topic is presented in an easily understood style and format which facilitate the comprehension of recent developments in heart valve replacement for the busy clinician.

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773 **Value of Intraoperative Left Ventricular Microbubbles Detected by Transesophageal Two-Dimensional Echocardiography in Predicting Neurologic Outcome After Cardiac Operations**

ERIC J. TOPOL, LINDA S. HUMPHREY, A. MICHAEL BORKON, WILLIAM A. BAUMGARTNER, DEBRA L. DORSEY, BRUCE A. REITZ, and JAMES L. WEISS

To determine whether the presence or absence of left ventricular intracavitary microbubbles during cardiac surgery predicts neurologic outcome, 82 patients undergoing cardiac surgery were studied with transesophageal 2-dimensional echocardiography. Microbubbles were detected after cardiopulmonary bypass in 34 patients (41%) and were more often found in those who underwent valvular or intracardiac manipulations than in those who underwent coronary revascularization, 30 of 40 vs 4 of 42 patients, respectively ($p < 0.001$). When dense microbubbles were identified (22 of 34 patients), mechanical attempts to eradicate them were not successful. Postoperative follow-up did not reveal new focal neurologic deficits. However, a prolonged confusional state (longer than 72 hours) occurred in 4 of 48 patients with no detectable microbubbles and 3 of 34 patients with microbubbles (difference not significant). Thus, intracavitary left ventricular microbubbles are detected frequently during cardiac surgery, particularly during valve replacement, but are not predictive of postoperative neurologic complications.

776 **Right Ventricular Ejection Fraction Measured by First-Pass Intravenous Krypton-81m: Reproducibility and Comparison with Technetium-99m**

DEAN F. WONG, T.K. NATARAJAN, WARREN SUMMER, PAUL A. TIBBITS, THOMAS BECK, DANIEL KOLLER, WAYNE KASECAMP, JAMES LAMB, JOSEPH OLYNYK, MARY SUE PHILP, MARSHALL BRYAN, and HENRY N. WAGNER, Jr.

Right ventricular ejection fraction was studied using intravenous first-pass krypton-81m in 22 subjects. This technique was compared with the standard technetium-99m method. Krypton-81m, which has a 13-second half-life, offers the advantage of multiple replicate studies within minutes of each other. The study showed good correlation of krypton-81m with the standard technique, but krypton-81m results in considerably less radiation exposure.

781 **Measurement of Left Ventricular Volume Using Single-Photon Emission Computed Tomography**

GARY R. CAPUTO, MICHAEL M. GRAHAM, KIRK D. BRUST, J. WARD KENNEDY, and WIL B. NELP

Left ventricular (LV) volume was measured using single-photon emission computed tomography (SPECT) of the cardiac blood pool. The tomographic slices were used to determine the counts per milliliter in the center of the left ventricle and total LV counts, which were used to derive mean LV volume. End-diastolic and end-systolic volumes were calculated from the mean volume using the LV time-activity curve from planar gated blood pool images. Phantom evaluation with simulated LV volumes (50 to 400 ml) showed excellent accuracy. For clinical validation, the results from 30 patients were compared with single-plane cineangiography. For end-diastolic and end-systolic volumes combined, the correlation with cineangiography showed a standard error of the estimate of 24 ml and 14 ml, respectively. This relatively simple, SPECT-based technique is an accurate and reproducible way to measure LV volume.

BRIEF REPORTS

787 **Echocardiographic Detection of Complete and Partial Papillary Muscle Rupture During Acute Myocardial Infarction**

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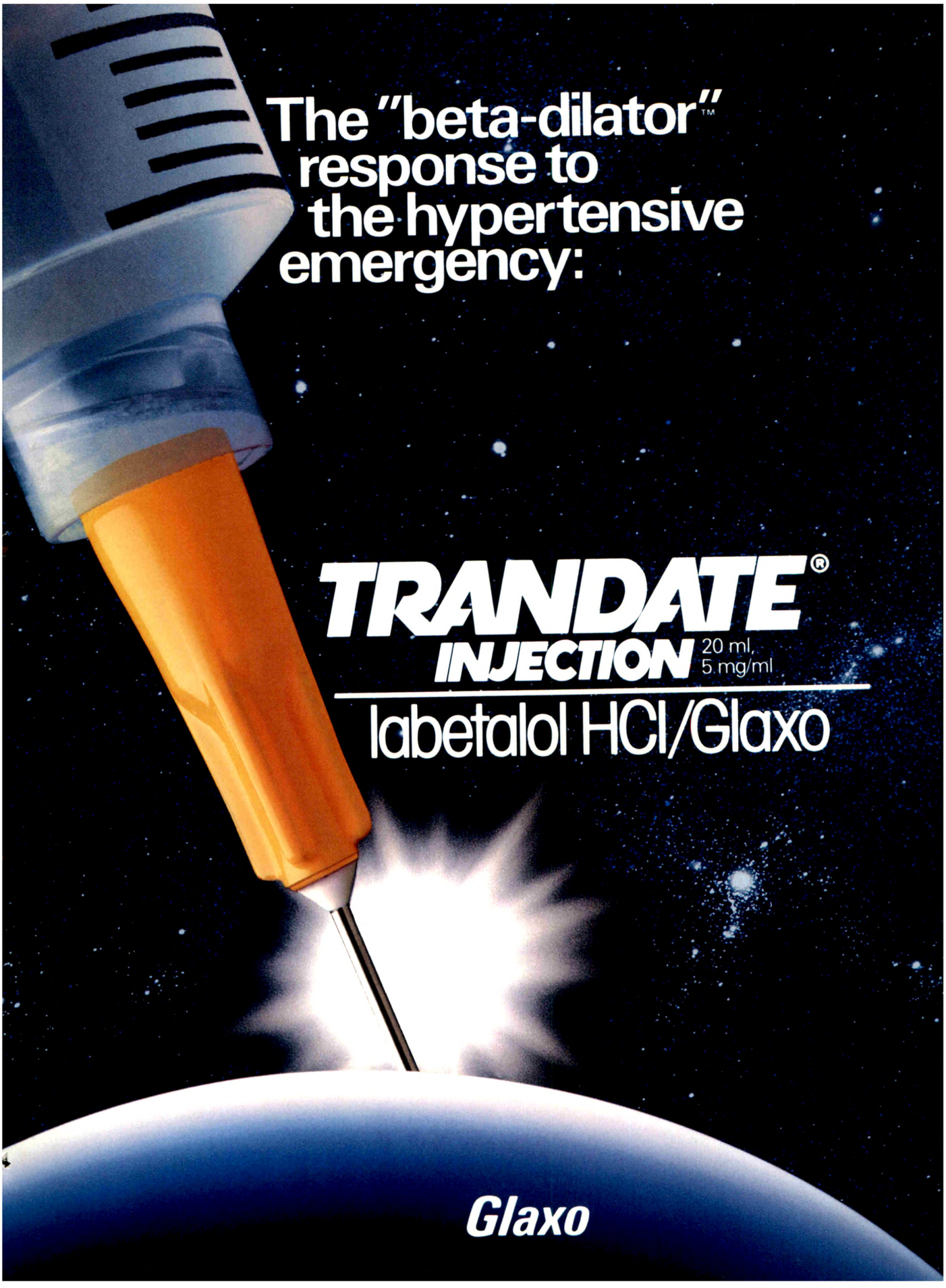
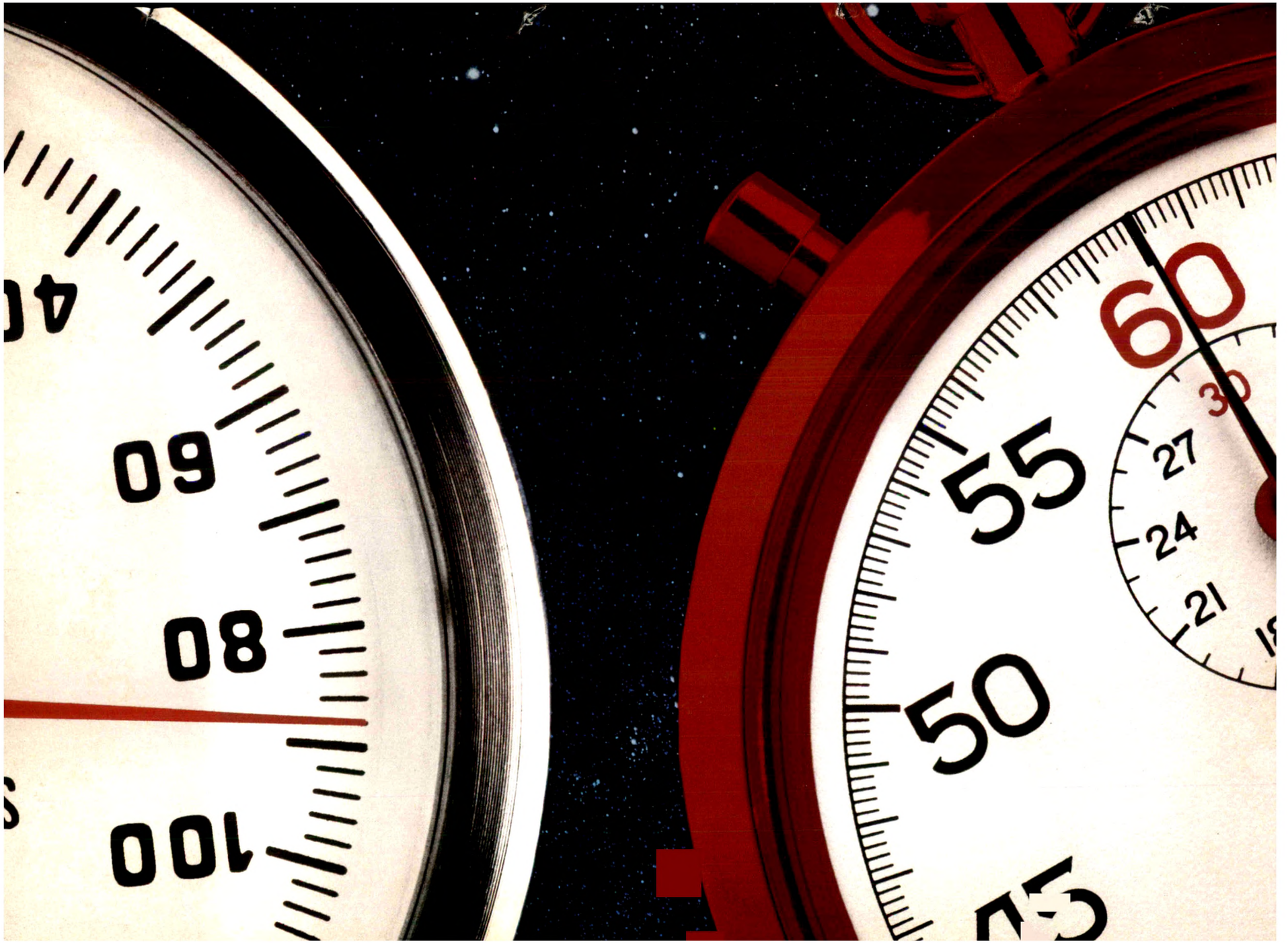

The "beta-dilator"™ response to the hypertensive emergency:
TRANDATE®
INJECTION 20 ml, 5 mg/ml
labetalol HCl/Glaxo
Glaxo


60
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For hypertensive emergency

TRANDATE®
INJECTION 20 ml, 5 mg/ml

labetalol HCl/Glaxo

The "beta-dilator"™ response: control within minutes

Action within a minute. Trandate® (labetalol HCl/Glaxo) Injection rapidly, predictably lowers blood pressure by lowering total peripheral resistance (TPR), while maintaining cardiac output.[1,2] The "beta-dilator"™ effect of simultaneous beta blockade and alpha blockade-induced vasodilation is apparent within a minute.

Rapid control. Full effect of an IV dose is apparent in 5 to 10 minutes: helps avoid hypotensive "overshoot," facilitates monitoring.

Cost control. Rapid effect may shorten hospital stay and beneficially affect costs under DRG's.

Well tolerated.* The most commonly reported adverse reactions: postural hypotension,† dizziness,† paresthesias, increased sweating and nausea.

Smooth transition to oral therapy with the same agent. Control of hypertensive crisis with Trandate Injection allows continued control on oral therapy with no need to change agents.

Trandate Injection—the "beta-dilator"™ response to hypertensive emergencies...another original product of Glaxo research.

* Patients should always be kept in a supine position during IV drug administration. See **DOSAGE AND ADMINISTRATION** section of Prescribing Information before initiating therapy.

† The episodes of postural hypotension and dizziness occurred primarily in one study in which patients were placed in an upright position within three hours of dosing for evaluation.

For a discussion of **ADVERSE REACTIONS**, please see Brief Summary of Prescribing Information on the last page of this advertisement.

Glaxo

For hypertensive emergency

TRANDATE® INJECTION 20 ml, 5 mg/ml

labetalol HCl/Glaxo

The "beta-dilator"™ response: control within minutes

- Trandate Injection can be administered as repeated IV injections, or by continuous infusion
- After initial dosing, further blood pressure reductions can be achieved with additional injections or by slow continuous infusion
- Discontinue Trandate Injection when blood pressure goal is achieved—when supine blood pressure has begun to rise, oral therapy may be initiated
- Patients should be kept in the supine position during IV drug administration. See **DOSAGE AND ADMINISTRATION** section of Prescribing Information before initiating therapy

For a discussion of **ADVERSE REACTIONS**, please see Brief Summary of Prescribing Information on the last page of this advertisement.

References: 1. Wallin JD, O'Neill WM Jr: Labetalol, current research and therapeutic status. *Arch Intern Med* 1983; 143:485-490. **2.** MacCarthy EP, Bloomfield S: Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. *Pharmacotherapy* 1983;3(4):193-219.

Glaxo

Glaxo Inc., Research Triangle Park, NC 27709

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TRN 138 Printed in U.S.A. March 1985

TRANDATE® Injection
(labetalol hydrochloride)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: TRANDATE® (labetalol HCl) Injection is indicated for control of blood pressure in severe hypertension.

CONTRAINDICATIONS: TRANDATE® Injection is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitilization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Ischemic Heart Disease: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TRANDATE is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.

Nonallergic Bronchospasm (eg, chronic bronchitis and emphysema): Since TRANDATE Injection at the usual intravenous therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.

Pheochromocytoma: Intravenous labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

Rapid Decreases of Blood Pressure: Caution must be observed when reducing severely elevated blood pressure. Although such findings have not been reported with intravenous labetalol HCl, a number of adverse reactions, including cerebral infarction, optic nerve infarction, angina and ischemic changes in the electrocardiogram, have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as 1 or 2 days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

PRECAUTIONS: General: ***Impaired hepatic function*** may diminish metabolism of TRANDATE® Injection.

Hypotension: Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

Jaundice or Hepatic Dysfunction: On rare occasions, oral labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) TRANDATE Injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.

When the patient is started on TRANDATE Tablets, following adequate control of blood pressure with TRANDATE Injection, appropriate directions for titration of dosage should be provided (see **DOSAGE AND ADMINISTRATION**).

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted: While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: Routine laboratory tests are ordinarily not required before or after intravenous labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: Since TRANDATE (labetalol HCl) Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C: Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the MRHD, respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE® (labetalol HCl) Injection is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: TRANDATE® Injection is usually well tolerated. Most adverse effects have been mild and transient and, in controlled trials involving 92 patients, did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with TRANDATE Injection with the incidence per 100 patients as noted:

Cardiovascular System: Ventricular arrhythmia in 1.

Central and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/skin in 7; hypoesthesia (numbness) and vertigo in 1 each.

Gastrointestinal System: Nausea in 13; vomiting in 4; dyspepsia and taste distortion in 1 each.

Metabolic Disorders: Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.

Psychiatric Disorders: Somnolence/yawning in 3.

Respiratory System: Wheezing in 1.

Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see TRANDATE Tablet Product Information for details.) Certain of the side effects increased with increasing oral dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are probably or possibly dose-related.

Labetalol HCl Daily Dose (mg)	**200**	**300**	**400**	**600**	**800**	**900**	**1200**	**1600**	**2400**
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	2	3	3	3	5	1	9	13	16
Fatigue	2	1	4	4	5	3	7	6	10
Nausea	<1	0	1	2	4	0	7	11	19
Vomiting	0	0	<1	<1	<1	0	1	2	3
Dyspepsia	1	0	2	1	1	0	2	2	4
Paresthesias	2	0	2	2	1	1	2	5	5
Nasal Stuffiness	1	1	2	2	2	2	4	5	6
Ejaculation Failure	0	2	1	2	3	0	4	3	5
Impotence	1	1	1	1	2	4	3	4	3
Edema	1	0	1	1	1	0	1	2	2

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl during investigational use and extensive foreign marketing experience.

Clinical Laboratory Tests: Among patients dosed with TRANDATE Tablets, there have been reversible increases of serum transaminases in 4% of patients tested and, more rarely, reversible increases in blood urea.

OVERDOSAGE: Overdosage with TRANDATE® Injection causes excessive hypotension which is posture sensitive and, sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: **Excessive bradycardia**—administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac failure**—administer a digitalis glycoside and a diuretic. **Hypotension**—administer vasopressors, eg, norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. **Bronchospasm**—administer a $beta_2$-stimulating agent and/or a theophylline preparation.

If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION: Initiation of Dosing with TRANDATE Tablets: Subsequent oral dosing with TRANDATE Tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 mg or 400 mg, depending on the blood pressure response. Thereafter, **inpatient titration with TRANDATE Tablets may proceed as follows:**

Inpatient Titration Instructions

Regimen	Daily Dose*
200 mg bid	400 mg
400 mg bid	800 mg
800 mg bid	1600 mg
1200 mg bid	2400 mg

*If needed, the total daily dose may be given in three divided doses.

While in the hospital, the dosage of TRANDATE (labetalol HCl) Tablets may be increased at one-day intervals to achieve the desired blood pressure reduction.

For subsequent outpatient titration or maintenance dosing see TRANDATE Tablets Product Information **DOSAGE AND ADMINISTRATION** for additional recommendations.

HOW SUPPLIED: TRANDATE® Injection, 5 mg/ml, is supplied in 20 ml (100 mg) ampules, box of 1 (NDC 0173-0350-59).

Store between 2° and 30° C (36° and 86° F.) Do not freeze.

Manufactured for Glaxo Inc. Research Triangle Park, NC 27709
by Schering Pharmaceutical Corporation (PR), Manati, PR 00701

October 1984

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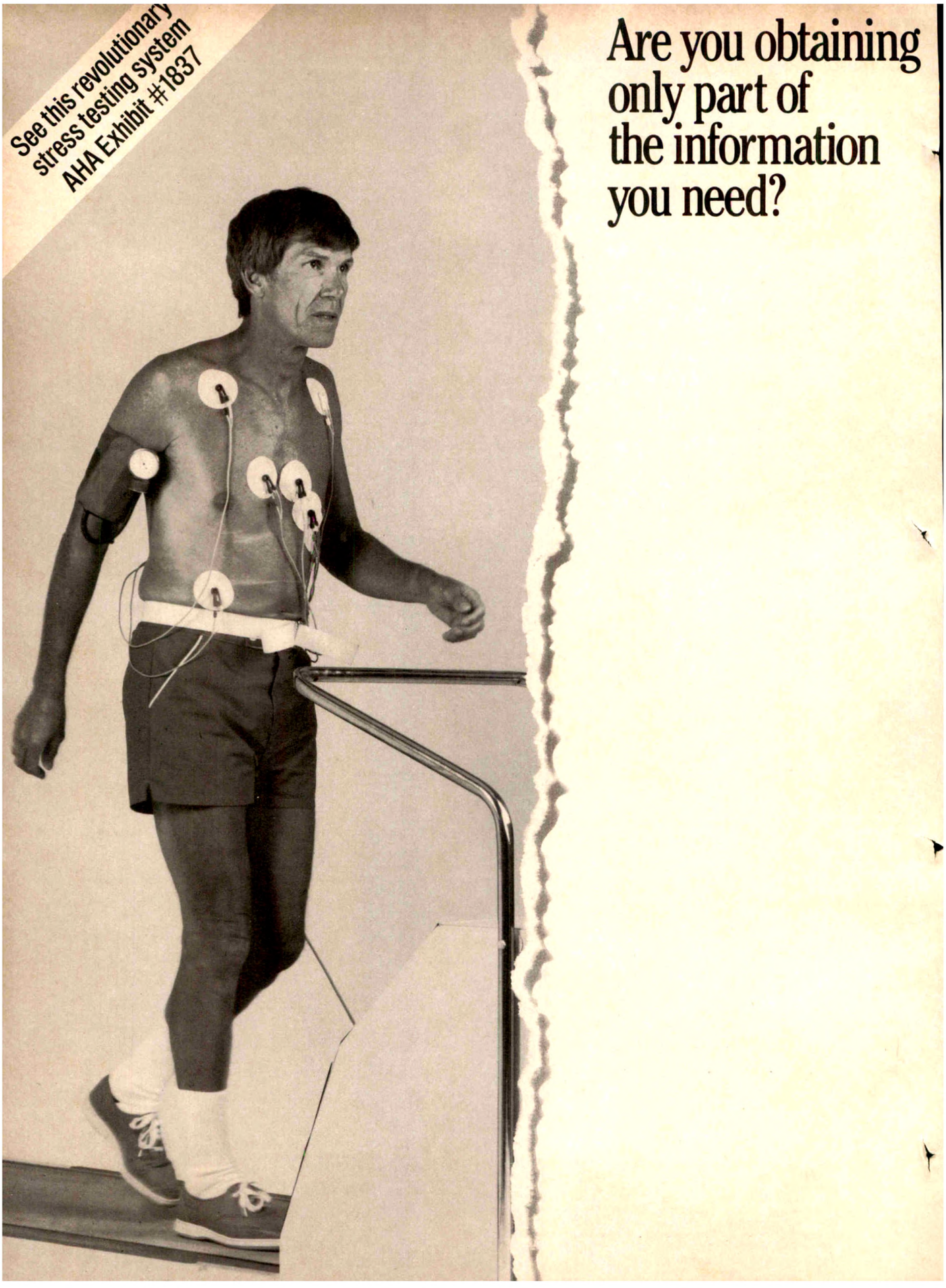
Glaxo

Glaxo, Inc., Research Triangle Park, NC 27709



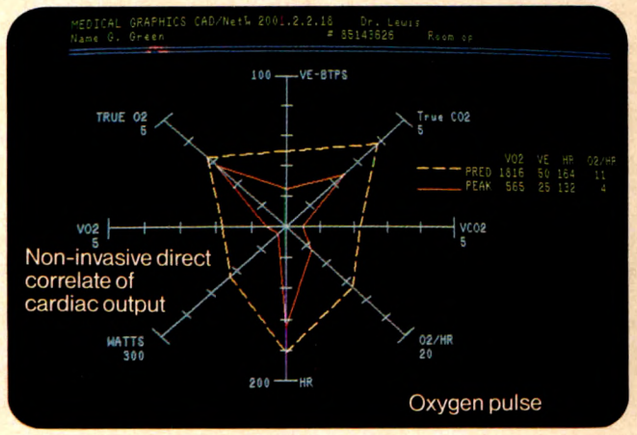
Are you obtaining only part of the information you need?

Medical Graphics System 2001 cardiodynamic imaging provides more, for comprehensive stress testing.

Stress testing is revolutionized with the CAD/Net™ Exercise Stress Testing System 2001 for non-invasive assessment of cardiac function. Real-time cardiodynamic imaging provides more clinically useful information about functional capacity and cardiac function than conventional stress testing methods.

Use the System 2001 simultaneously with your existing EKG and treadmill or cycle ergometer for:

- Early detection of coronary atherosclerosis, valvular and/or congestive heart disease (functional class impairment)
- Cardiac rehabilitation of CAB or PTCA patients (assessment of functional class improvement and patient prognosis)
- Evaluation of exercise effects of various pharmacologic agents for treatment of hypertension, congestive heart failure, coronary artery disease, arrhythmias, etc.
- Differentiation of cardiac versus pulmonary induced dyspnea and angina during exercise



Cardiodynamic Image ™

Patient Case: 56 year old with CHF. Note severe functional impairment upon limited exertion (class C), as indicated by a significantly depressed **V̇02** and **02 pulse** with compensatory HR increase.

Convenient, clinically applicable.

The automated System 2001 conducts the stress test protocol allowing physician/patient interaction. Real-time test results are immediately available on the cardiodynamic image screen in an easy to interpret graphic format. And, they can be stored for comparison with subsequent patient follow-up tests. The System 2001 saves both time and money.

The System 2001—a revolution in exercise testing.

For more information on how to maximize clinically useful data and make every stress test count, call us toll-free at **1-800-328-4138** or, return the coupon below.

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Please send me: ☐ Product literature ☐ On-site demonstration information ☐ Exercise seminar dates and papers on the clinical application of this system in cardiology

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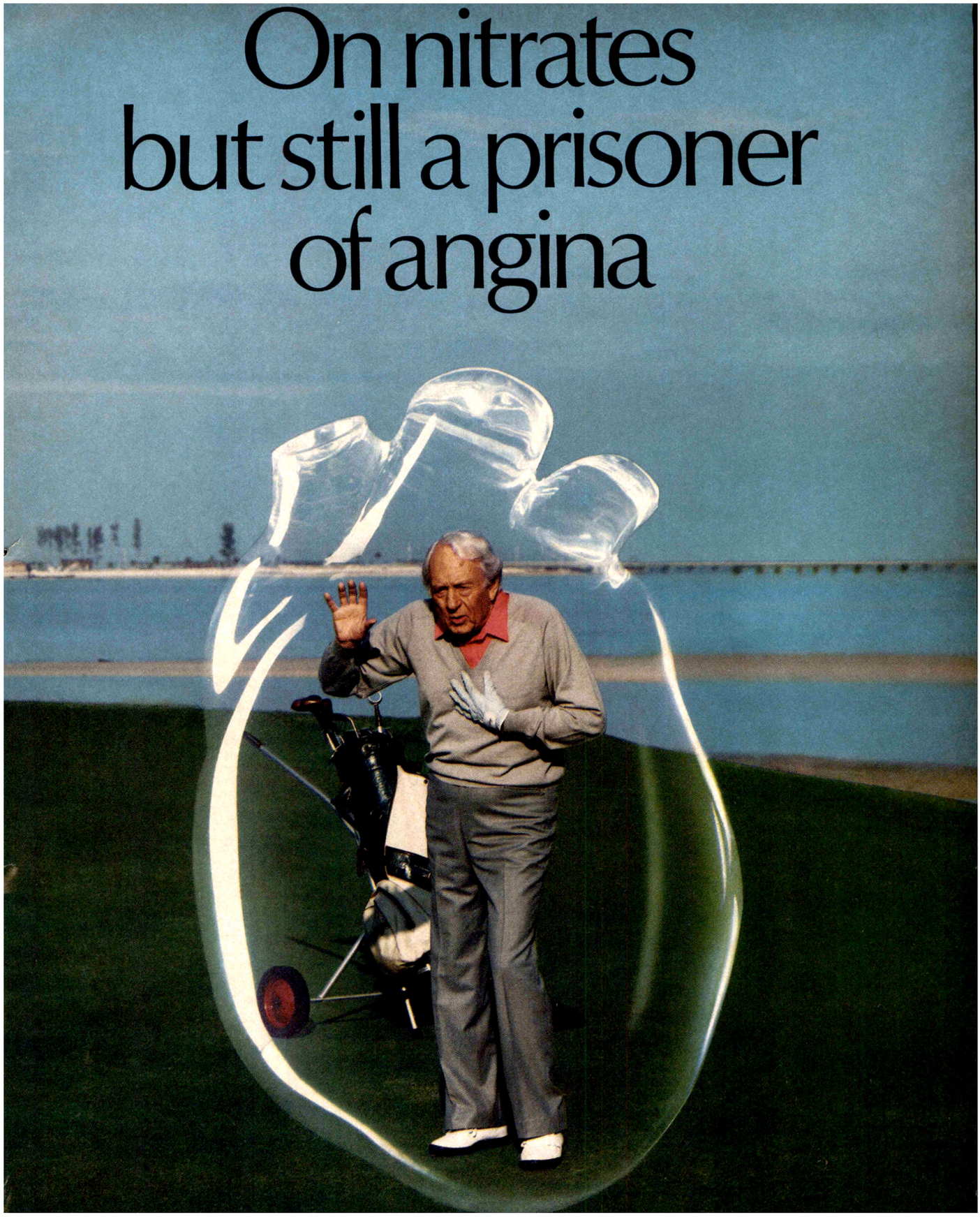
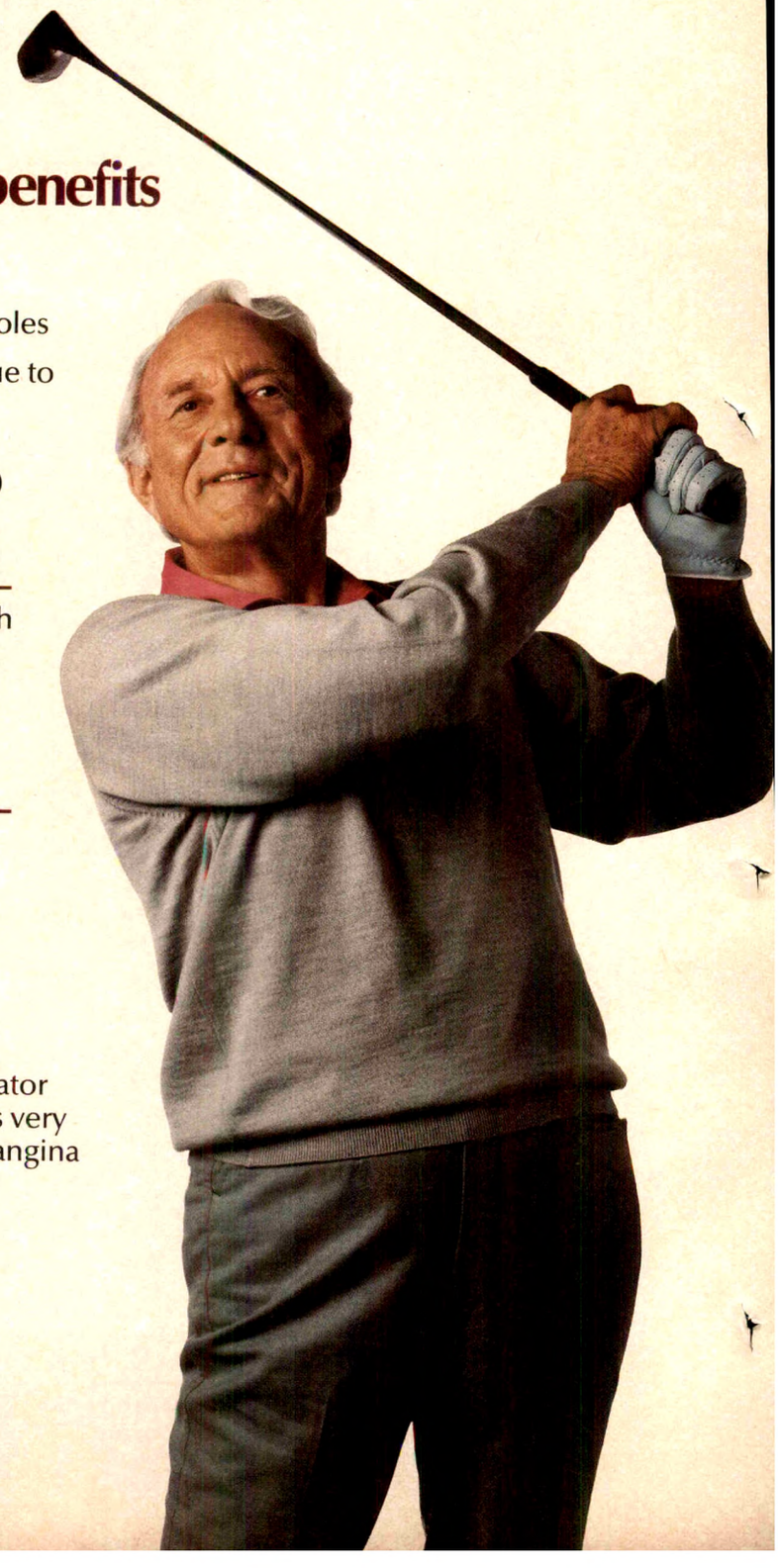
On nitrates but still a prisoner of angina



When nitrates alone are not enough

Add **Calan®** TABLETS
80 mg and 120 mg
(verapamil HCl)



Calan plus nitrates: Unique hemodynamic benefits

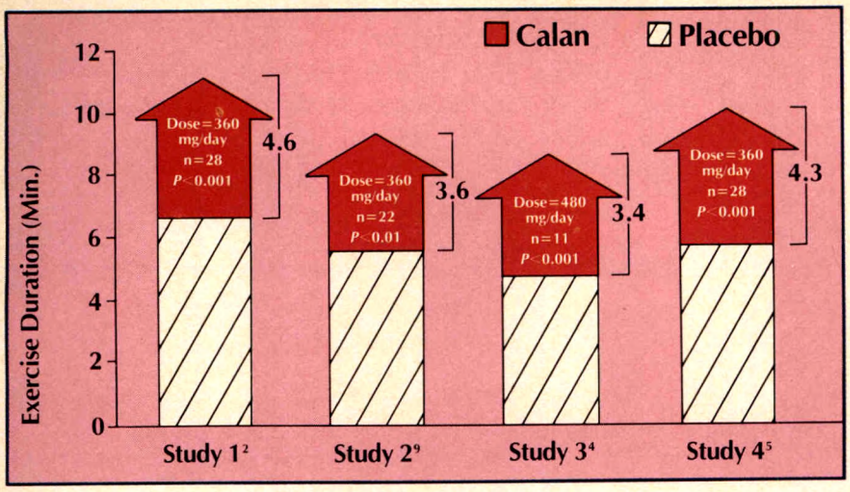
- increased myocardial oxygen supply—prevents vasoconstriction both in large coronary arteries and in coronary arterioles
- reduced myocardial oxygen demand due to
  - —a reduction in peripheral vascular resistance (afterload)
  - —a decrease in venous return (preload)
  - —a modest decrease in contractility

"It makes sense to treat those patients [with chronic stable angina]... [with] an agent that has a beneficial effect on both oxygen demand and supply, rather than a beta blocker which attacks just one side of that ratio."[1]

Calan plus nitrates: Efficacy for all types of angina

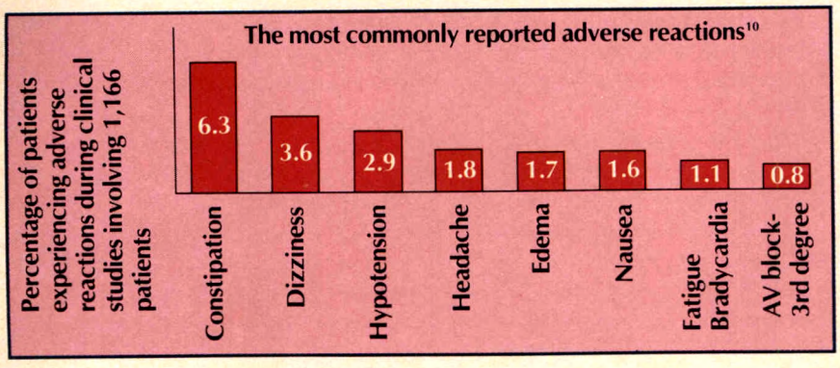
"...a combination of rate-lowering vasodilator (verapamil...) and long-acting nitrates...is very efficacious in patients with variant angina, angina of effort, and unstable angina at rest."[1]

Calan efficacy: Significant improvement in exercise tolerance[2-9]



- clinically significant improvement in exercise tolerance
- clinically significant reduction in the number of attacks and the need for sublingual nitroglycerin

Calan safety: Favorable side-effects profile



With Calan, side effects such as fatigue, mental depression, impotence or bradycardia (heart rate less than 50 beats/min) seldom occur.

In one study involving 63 patients "verapamil therapy was not discontinued in any patient because of the development of adverse reactions."[8]

Calan® *TABLETS*
80 mg and 120 mg
(verapamil HCl)

References:

1. Hillis, D., in Hillis, D. (Moderator); Frishman, W.; Leon, M.; Packer, M.; Robertson, R. M.; Subramanian, B., and Winniford, M. (Discussants): The Expanding Role of Calcium Channel Blockers, 1984. **2.** Subramanian, B., and others: Long-Term Antianginal Action of Verapamil Assessed with Quantitated Serial Treadmill Stress Testing, Am. J. Cardiol. *48*: 529-535 (Sept.) 1981. **3.** Subramanian, B.: Long-Term Therapy of Angina with Calcium Antagonists, Cardiovasc. Rev. Rep. *4*:493-497 (April) 1983. **4.** Leon, M.B.: Combination Therapy Using Calcium-Channel Blockers and Beta Blockers in Patients with Chronic Stable Angina Pectoris, Cardiovasc. Rev. Rep. *4*:171-177 (Feb.) 1983. **5.** Subramanian, V. B., and others: Rationale for the Choice of Calcium Antagonists in Chronic Stable Angina: An Objective Double-Blind Placebo-Controlled Comparison of Nifedipine and Verapamil, Am. J. Cardiol. *50*:1173-1179 (Nov.) 1982. **6.** Weiner, D. A., and others: Efficacy and Safety of Verapamil in Patients With Angina Pectoris After 1 Year of Continuous, High-Dose Therapy, Am. J. Cardiol. *51*:1251-1255 (May 1) 1983. **7.** Frishman, W. H., and others: Superiority of Verapamil to Propranolol in Stable Angina Pectoris: A Double-blind, Randomized Crossover Trial, Circulation *65* (Suppl. 1):51-59 (Jan.) 1982. **8.** Scheidt, S., and others: Long-Term Effectiveness of Verapamil in Stable and Unstable Angina Pectoris: One-Year Follow-Up of Patients Treated in Placebo-Controlled Double-Blind Randomized Clinical Trials, Am. J. Cardiol. *50*:1185-1190 (Nov.) 1982. **9.** Bowles, M. J., and others: Double-blind Randomized Crossover Trial of Verapamil and Propranolol in Chronic Stable Angina, Am. Heart J. *106*:1297-1306 (Dec.) 1983. **10.** Product Labeling.

SEARLE

Please see following page for a brief summary of the complete prescribing information.

5W001T

Calan® TABLETS
80 mg and 120 mg
(verapamil HCl)

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block.

Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension, usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Elevations of liver enzymes have been reported. Four cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Patients with atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) may develop a very rapid ventricular response after receiving verapamil (or digitalis). Treatment is usually DC-cardioversion. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in less than 0.5% of patients, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions, spotty menstruation, ecchymosis, bruising, gynecomastia, and psychotic symptoms. Overall continuation rate was 94.5% in 1,166 patients.

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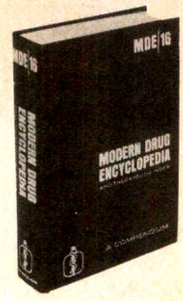

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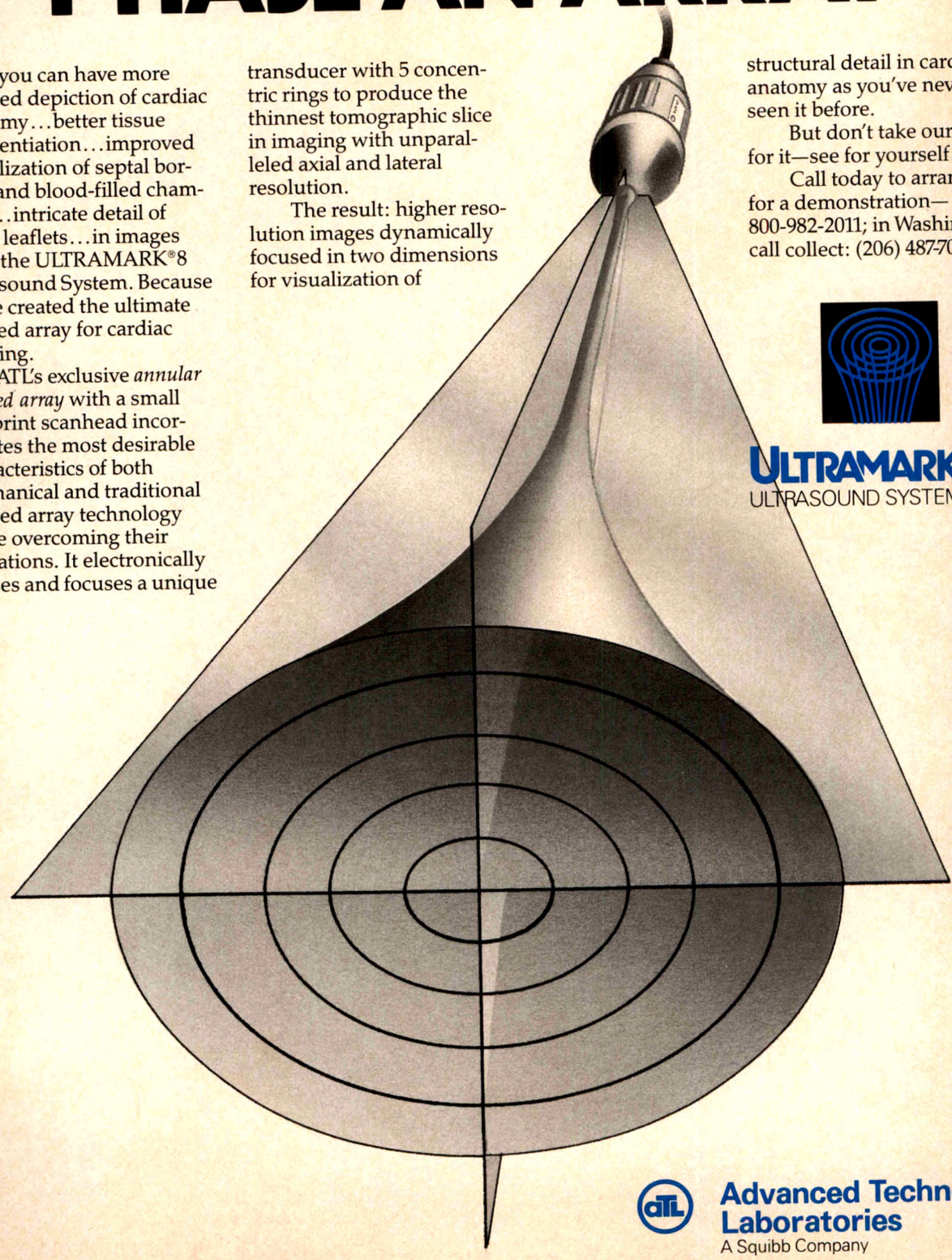

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834 **Echocardiographic Detection of Circulating Blood in Normal Canine Hearts**
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AJC 25 YEARS AGO

837 **The AJC in November 1960**
WILLIAM C. ROBERTS

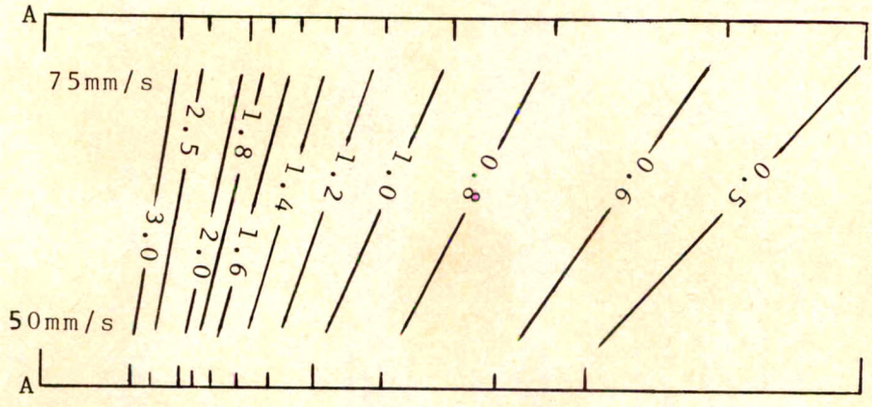
838 **FROM THE EDITOR**

CME Test on page 760

INSTRUCTIONS TO AUTHORS on page 820

CORRECTION

In the September 1, 1985 issue on page 489 (Simplified Doppler Estimation of Mitral Valve Area [S. S. Yang and H. Goldberg]), Figure 2 was incorrectly scaled. The correct size appears below and can now be applied to Figure 1 of that report.



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All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA. (See Brief Summary of Prescribing Information on the following page.)

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Transderm-Nitro®
nitroglycerin
Transdermal Therapeutic System

Brief Summary (For Full Prescribing Information, See Package Insert)

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.
Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.
Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area. Transderm-Nitro system should not be applied to the distal parts of the extremities.
The usual dosage is one Transderm-Nitro 5 system every 24 hours. Some patients, however, may require the Transderm-Nitro 10 system. If a single Transderm-Nitro 5 system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 systems or one Transderm-Nitro 10 system. More systems may be added as indicated by continued careful monitoring of clinical response. The Transderm-Nitro 2.5 system is useful principally for decreasing the dosage gradually, though it may provide adequate therapy for some patients when used alone.
The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.
Do not store above 86°F (30°C).

PATIENT INSTRUCTIONS FOR APPLICATIONS
A patient leaflet is supplied with the systems.

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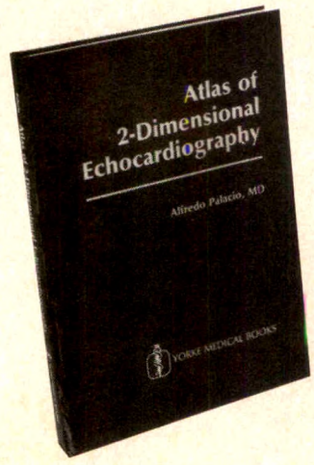

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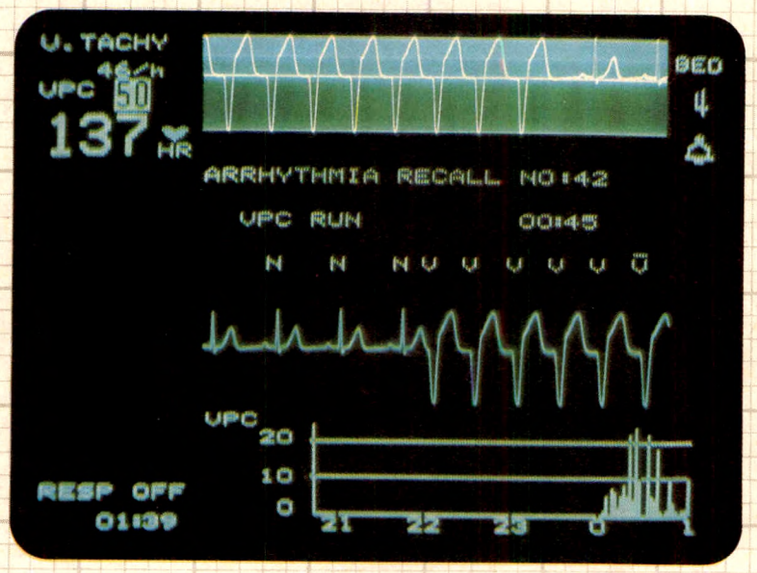


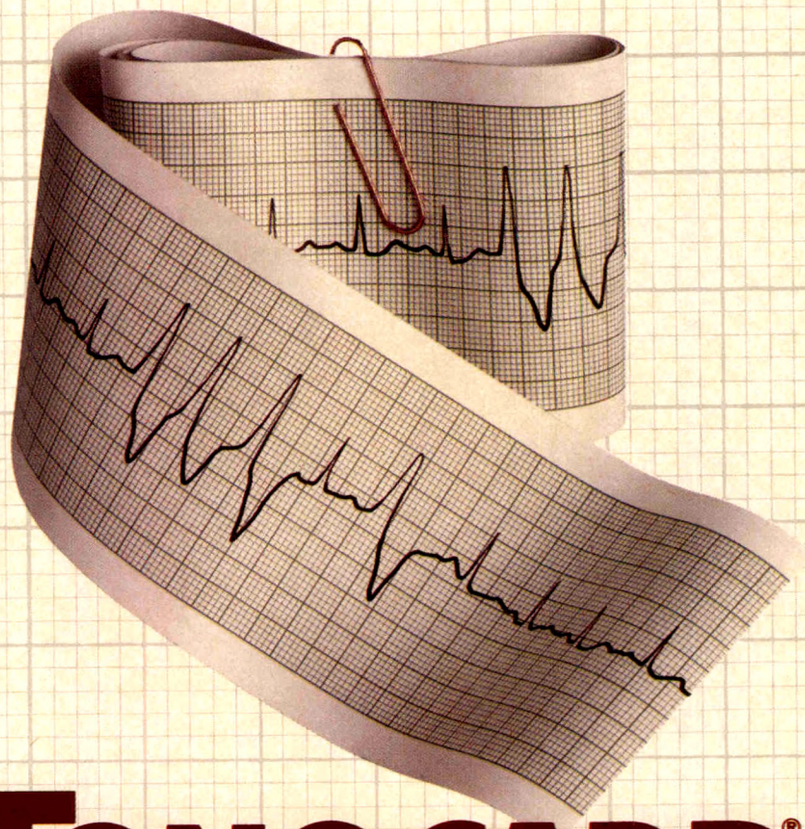
Like other antiarrhythmics, tocainide has not been shown to prevent sudden death, and also, like other antiarrhythmics, it has potentially serious adverse effects including the ability to worsen arrhythmias. Clinical and electrocardiographic evaluation should be used to periodically assess the need for therapy.

TONOCARD® (Tocainide HCl, MSD) is contraindicated in patients who are hypersensitive to this product or to local anesthetics of the amide type and in patients with second- or third-degree atrioventricular block in the absence of an artificial ventricular pacemaker.

Agranulocytosis, bone marrow depression, leukopenia, hypoplastic anemia, and thrombocytopenia have been reported in patients receiving TONOCARD; fatalities have occurred. Blood counts are recommended within the first two to three weeks of therapy and periodically thereafter. See Prescribing Information for details.

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

TONOCARD in the office.



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Like other antiarrhythmics, tocainide has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given tocainide be evaluated electrocardiographically and clinically prior to, and during, tocainide therapy to determine whether the response to tocainide supports continued treatment.

CONTRAINDICATIONS

Patients who are hypersensitive to this product or to local anesthetics of the amide type.

Patients with second or third degree atrioventricular block in the absence of an artificial ventricular pacemaker.

WARNINGS

Blood Dyscrasias: Agranulocytosis, bone marrow depression, leukopenia, hypoplastic anemia and thrombocytopenia have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill and who were receiving concomitant drugs; fatalities have occurred. Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that blood counts, including differential and platelet counts, be performed at least once within the first two to three weeks of therapy; and periodically thereafter, particularly within the first three months of therapy. Blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat, or stomatitis), bruising, or bleeding. If any of these hematologic disorders is identified, TONOCARD should be discontinued and appropriate treatment should be instituted if necessary. Blood counts usually return to normal within one month of discontinuation. Caution should be used in patients with preexisting marrow failure or cytopenia of any type. (See ADVERSE REACTIONS).

Acceleration of Ventricular Rate: Acceleration of ventricular rate occurs infrequently when antiarrhythmics are administered to patients with atrial flutter or fibrillation (see ADVERSE REACTIONS).

PRECAUTIONS

General

Pulmonary Fibrosis: Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill. The experiences are usually characterized by bilateral infiltrates on x-ray and are frequently associated with dyspnea and cough. Fever may or may not be present. Patients should be instructed to promptly report the development of any pulmonary symptoms such as exertional dyspnea, cough or wheezing. Chest x-rays are advisable at that time. If these pulmonary disorders develop, TONOCARD should be discontinued. (See ADVERSE REACTIONS).

In patients with known heart failure or minimal cardiac reserve, TONOCARD should be used with caution because of the potential for aggravating the degree of heart failure.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing depression of cardiac conductivity.

In patients with severe liver or kidney disease, the rate of drug elimination may be significantly decreased (see DOSAGE AND ADMINISTRATION).

Since antiarrhythmic drugs may be ineffective in patients with hypokalemia, the possibility of a potassium deficit should be explored and, if present, the deficit should be corrected.

Like all other oral antiarrhythmics, TONOCARD has been reported to increase arrhythmias in some patients (see ADVERSE REACTIONS).

Information for Patients

Patients should be instructed to promptly report the development of bruising or bleeding; any signs of infections such as fever, chills, sore throat, or soreness and ulcers in the mouth; or any pulmonary symptoms, such as exertional dyspnea, cough, or wheezing.

Laboratory Tests

As with other antiarrhythmics, abnormal liver function tests, particularly in the early stages of therapy, have been reported. Periodic monitoring of liver function should be considered. Hepatitis and jaundice have been reported in some patients.

Drug Interactions

Specific interaction studies with digoxin and metoprolol have been conducted, no clinically significant interaction was seen with digoxin, but tocainide and metaprolol had additive effects on wedge pressure and cardiac index. TONOCARD has also been used in open studies with digitalis, beta-blocking agents, other antiarrhythmic agents, anticoagulants, and diuretics, without evidence of clinically significant interactions. Nevertheless, caution should be exercised in the use of multiple drug therapy.

TONOCARD is equally effective in digitalized and non-digitalized patients. In 17 patients with refractory ventricular arrhythmias on concomitant therapy, serum digoxin levels (1.1 ± 0.4 ng/mL) remained in the expected normal range (0.5-2.5 ng/mL) during tocainide administration.

Pregnancy

Pregnancy Category C. In a teratogenicity study in rabbits, tocainide was administered orally at doses of 25, 50, and 100 mg/kg/day (about 1 to 4 times the usual human dose). No evidence of a drug-related teratogenic effect was noted; however, these doses were maternotoxic and produced a dose-related increase in abortions and stillbirths. In a teratogenicity study in rats, an oral dose of 300 mg/kg/day (about 12 times the usual human dose) showed no evidence of treatment-related fetal malformations, but maternotoxicity and an increase in fetal resorptions were noted. An oral dose of 30 mg/kg/day (about twice the usual human dose) did not produce any adverse effects.

In reproduction studies in rats at maternotoxic oral doses of 200 and 300 mg/kg/day (about 8 and 12 times the usual human dose, respectively), dystocia, and delayed parturition occurred which was accompanied by an increase in stillbirths and decreased survival in offspring during the first week postpartum. Growth and viability of surviving offspring were not affected for the remainder of the lactation period.

There are no adequate and well-controlled studies in pregnant women. TONOCARD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether tocainide is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from TONOCARD, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

TONOCARD commonly produces minor, transient, nervous system and gastrointestinal adverse reactions, but is otherwise generally well tolerated. TONOCARD has been evaluated in both short-term (n = 1,358) and long-term (n = 262) controlled studies as well as a compassionate use program. Dosages were lower in most of the controlled studies (1200 mg/day) and higher in the compassionate use program (1800 mg and more). In long-term (2-6 months) controlled studies, the most frequent adverse reactions were lightheadedness/dizziness (15.3 percent), nausea (14.5 percent), paresthesia/numbness (9.2 percent), and tremor (8.4 percent). These reactions were generally mild, transient, dose-related and reversible with a reduction in dosage, by taking the drug with food, or by therapy discontinuation. Tremor, when present, may be useful as a clinical indicator that the maximum dose is being approached. Adverse reactions leading to therapy discontinuation occurred in 21 percent of patients in long-term controlled trials and were usually related to the nervous system or gastrointestinal system.

Adverse reactions occurring in greater than one percent of patients from the short-term and long-term controlled studies appear in the following table:

	Percent of Patients Controlled Studies	
	Short-term (n = 1,358)	Long-term (n = 262)
NERVOUS SYSTEM		
Lightheadedness/dizziness/vertigo/giddiness	8.0	15.3
Parasthesia/numbness	3.5	9.2
Tremor/quivering/tremulousness	2.9	8.4
Confusion/disorientation/hallucinations	2.1	2.7
Altered mood/awareness	1.5	3.4
Restlessness/shakiness/nervousness	1.5	0.4
Blurred vision/visual disturbances	1.3	1.5
Discoordination/unsteadiness/walking disturbances	1.2	0.0
Anxiety	1.1	1.5
Tinnitus/hearing loss	0.4	1.5
Ataxia	0.2	3.0
Nystagmus	0.0	1.1
GASTROINTESTINAL SYSTEM		
Nausea	15.2	14.5
Vomiting	8.3	4.6
Anorexia	1.2	1.9
Diarrhea/loose stools	0.0	3.8
CARDIOVASCULAR SYSTEM		
Hypotension	3.4	2.7
Bradycardia	1.8	0.4
Palpitations	1.8	0.4
Chest Pain	1.6	0.4
Conduction disturbances	1.5	0.0
Left ventricular failure	1.4	0.0
OTHER		
Sweating/cold sweat/night sweats/clammy	5.1	2.3
Headache	2.1	4.6
Tiredness/drowsiness/fatigue/lethargy/lassitude/sleepiness	1.6	0.8
Hot/cold feelings	0.5	1.5
Rash/skin lesion	0.4	8.4

An additional group of about 2,000 patients has been treated in a program allowing for the use of TONOCARD under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy, and comparatively high doses of TONOCARD were used. Fifty-four percent of the patients continued in the program for one year or longer, and 12 percent were treated for longer than three years, with the longest duration of therapy being nine years. Adverse reactions leading to therapy discontinuation occurred in 12 percent of patients (usually central nervous system effects or rash). A tabulation of adverse reactions occurring in one percent or more of patients follows:

	Percent of Patients Compassionate Use (n = 1,927)
NERVOUS SYSTEM	
Lightheadedness/dizziness/vertigo/giddiness	25.3
Tremor/quivering/tremulousness	21.6
Restlessness/shakiness/nervousness	11.5
Confusion/disorientation/hallucinations	11.2
Altered mood/awareness	11.0
Ataxia	10.8
Blurred vision/visual disturbances	10.0
Paresthesia/numbness	9.2
Nystagmus	1.1
GASTROINTESTINAL SYSTEM	
Nausea	24.6
Anorexia	11.3
Vomiting	9.0
Diarrhea/loose stools	6.8
CARDIOVASCULAR SYSTEM	
Increased ventricular arrhythmias/PVCs	10.9
CHF/progression of CHF	4.0
Tachycardia	3.2
Hypotension	1.8
Conduction disturbances	1.3
Bradycardia	1.0
OTHER	
Rash/skin lesion	12.2
Sweating/cold sweat/night sweats/clammy	8.3
Arthritis/arthralgia	4.7
Myalgia	1.7
Lupus	1.6

Adverse reactions occurring in less than one percent of patients in either the controlled studies or the compassionate use program or since the drug was marketed are as follows:

Nervous System: Coma, convulsions/seizures, depression, psychosis, mental change, agitation, altered taste/smell, difficulty concentrating, diplopia, dysarthria, impaired memory, increased stuttering/slurred speech, insomia/sleeping disturbance, local anesthesia, nightmares, thirst, weakness, myasthenia gravis.

Gastrointestinal System: Abnormal liver function tests, hepatitis, jaundice, (see PRECAUTIONS); stomatitis; abdominal pain/discomfort; constipation; dysphagia; gastrointestinal symptoms (including dyspepsia).

Cardiovascular System: Ventricular fibrillation, extension of acute myocardial infarction, cardiogenic shock, angina, AV block, hypertension, increased QRS duration, pleurisy/pericarditis, prolonged QT interval, right bundle branch block, syncope, vasovagal episodes, cardiomegaly, sinus arrest.

Pulmonary System: Respiratory arrest, pulmonary edema, pulmonary embolism, pulmonary fibrosis, fibrosing alveolitis, interstitial pneumonitis, pneumonia, dyspnea.

Other: Hematologic disorder (agranulocytosis, bone marrow depression, hypoplastic anemia, anemia, leukopenia, thrombocytopenia), increased ANA, urinary retention, polyuria/increased diuresis, alopecia, cinchonism, claudication, cold extremities, dry mouth, earache, edema, fever, hiccups, itching, leg cramps, malaise, metallic/menthol taste, muscle twitching/spasm, neck pain, pain radiating from neck, pallor/flushed face, pressure on shoulder, yawning.

Agranulocytosis, bone marrow depression, leukopenia, hypoplastic anemia, and thrombocytopenia have been reported (0.18 percent) in patients receiving TONOCARD in controlled trials and the compassionate use program. Many of these events occurred in patients who were seriously ill or who were receiving concomitant drugs; fatalities have occurred. Most of these events have been noted during the first 12 weeks of therapy. (See WARNINGS).

Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. The incidence of pulmonary fibrosis (including interstitial pneumonitis and fibrosing alveolitis) was 0.11 percent in controlled trials and the compassionate use program. These events usually occurred in seriously ill patients. Symptoms of these pulmonary disorders and/or x-ray changes usually occurred following 3-18 weeks of therapy and two patients died. (See PRECAUTIONS).

HOW SUPPLIED

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Effect of Intracoronary Thrombolytic Therapy on Exercise-Induced Ischemia After Acute Myocardial Infarction

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Intracoronary streptokinase (SK) therapy increases vessel patency rate after acute myocardial infarction (AMI) and thus may lead to a greater exercise-induced myocardial ischemia. This hypothesis was tested in 39 patients enrolled in an angiographically randomized trial of intracoronary SK (19 treated with SK and 20 control subjects); all patients underwent thallium-201 scintigraphy at rest before acute angiography, as well as at rest and during stress 5 to 6 weeks after AMI. The patients were classified into 2 groups based on the presence (n = 13) or absence (n = 26) of complete obstruction of the infarct-related coronary artery at the end of the acute angiography. Semiquantitative score of myocardial thallium uptake was expressed as percent of maximal defect score. Thallium defect score at rest between admission and 5 to 6 weeks' study decreased from 10 ± 16% units in the control group and from 23 ± 14% units in the SK group (p = 0.01). This decrease was related to opening of the infarct-related artery (opening 23 ± 16% vs occlusion 5 ± 10%). The change in exercise-induced defect score was significantly (p = 0.01) larger in patients in the SK group (11 ± 6% units) than in those in the control group (5 ± 7% units). The perfusion defect during exercise was larger (p = 0.006) in patients with incomplete obstruction or reperfusion (10 ± 6% units) than in patients with complete obstruction (3 ± 7%). This difference was independent of the number of diseased coronary vessels. Radionuclide ventriculography during submaximal exercise was performed within 2 to 3 weeks after AMI in 21 of the 39 patients studied. The exercise-induced increase in ejection fraction was significantly smaller in patients with opened vessels (4 ± 7%) than in those with closed vessels (13 ± 9%; p = 0.03). Thus, in this group of patients who were studied 5 to 6 weeks after AMI, patients treated with SK demonstrated scintigraphic improvement at rest compared with results at admission, but had more exercise-induced ischemia; this was related to incomplete coronary obstruction or reperfusion.

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In patients with evolving acute myocardial infarction (AMI), successful reperfusion can be achieved after thrombolysis with intracoronary streptokinase (SK).[1–4] However, residual high-grade stenoses frequently remain at the site of initial occlusion and may result in rethrombosis.[5,6] Furthermore, these residual stenoses may predispose the patient to persistent angina pectoris

or exercise-induced ischemia. We studied this latter possibility in patients enrolled in a randomized, angiographically controlled trial of intracoronary SK therapy. The patients studied were selected because they had undergone admission thallium scintigraphy and underwent scintigraphy at rest and during exercise 5 to 6 weeks after AMI. In this subset of patients, we analyzed the changes in perfusion scans at rest between admission and 5 to 6 weeks after AMI and compared these data with the exercise scintigrams obtained 5 to 6 weeks after AMI.

Methods

All patients included in a randomized trial of intracoronary SK between October 1981 and August 1984 were considered for the study. However, only those who underwent thallium scintigraphy at rest and during exercise 5 to 6 weeks after AMI were included in the present study. The protocol of the randomized trial has been described.[7] Eighty-three patients who presented to the hospital within 3 hours of the onset of chest pain were enrolled in the trial (41 in the control group and 42 in the SK group). The patients were retrospectively classified into 2 subgroups based on the angiographic absence or presence of complete obstruction of the infarct-related coronary artery. Three patients died in cardiogenic shock during the first 12 hours after admission. Three other patients died during the 2-month follow-up period. The 6 patients who died had a complete coronary artery obstruction (3 in the control group and 3 in the SK group). During the first 5 weeks after AMI, 1 patient (treated with SK) had a reinfarction and 4 patients underwent coronary artery bypass surgery (2 treated with SK and 2 control subjects). Six patients in the SK group and 2 in the control group underwent coronary balloon dilation. In the 12 patients who underwent surgical or angioplasty treatment, the infarct-related coronary artery was found to be patent. From the remaining 64 patients (34 in the control group and 30 in the SK group), 25 patients (14 control subjects and 11 treated with SK) did not undergo exercise testing combined with thallium imaging 5 to 6 weeks after AMI. Among these 25 patients, 6 (2 control subjects and 4 treated with SK) had typical symptoms of angina pectoris or positive electrocardiographic findings during exercise. These 6 patients had a patent infarct-related coronary artery.

The present study group comprised 39 patients (33 men, 6 women), aged 37 to 70 years (mean 55 ± 19). Two patients (1 treated with SK and 1 control subject) had a history of AMI. Diagnosis of AMI was based on typical prolonged chest pain at rest, lasting for more than 30 minutes and persistent ST-segment elevation of at least 2 mm in 3 or more leads of the standard 12-lead electrocardiogram. The final diagnosis of AMI was retrospectively confirmed from serial serum creatine kinase values. As soon as possible after the admission and inclusion in the randomized trial, 1.5 mCi of thallium-201 were intravenously injected. Ten minutes after injection of thallium-201, intravenous infusion of nitroglycerin was begun. Immediately after the initiation of nitrate therapy, thallium-201 imaging was begun and the acquisition of the 3 standard views was made within 30 minutes. Without taking into account the results of thallium-201 scintigraphy, patients were randomly assigned to a control group (n = 20) and an SK group (n = 19). After 10,000 units of intravenous heparin had been administered, coronary angiography was performed. The interval from the onset of infarct symptoms to angiography was 266 ± 152 minutes in the control group and 234 ± 50 minutes in the SK group. Nitroglycerin (500 μg) was injected into the coronary artery to exclude a coronary spasm. In the SK group, SK was infused into the coronary artery at a mean dose of 240,526 ± 45,761 IU within 45 minutes. Coronary angiography was repeated at the end of SK infusion to evaluate the success of recanalization and the residual stenosis at the site of occlusion. Intravenous heparin infusion (20,000 IU/day) was given for the first 2 days after catheterization. Oral nitrates were routinely given after withdrawal of intravenous infusion (2 to 4 days after beginning of infusion). All patients subsequently received antiplatelet agents (aspirin and dipyridamole) and calcium antagonist drugs.

Exercise protocols: All patients underwent maximal exercise combined with thallium-201 imaging 5 to 6 weeks after AMI. Twenty-one of the 39 patients also underwent radionuclide ventriculography during submaximal exercise 2 to 3 weeks after AMI.

Thallium scintigraphy during maximal exercise: The exercise tests were performed on a bicycle ergometer with an initial workload of 20 W; the exercise intensity was increased by 20 W every minute until the patient had typical anginal pain or until subjective exhaustion. Three Frank orthogonal leads were constantly monitored and recorded on paper every minute during exercise and the first 5 minutes of the recovery. A 20-second electrocardiographic sample was also recorded on a digital magnetic tape at the end of every minute, at rest, during the exercise and during the recovery. These digitized electrocardiographic samples were averaged and analyzed by computer (Modcomp 11/25) using an adapted version of the program of the Thoraxcenter in Rotterdam.[8] The amount of ST-segment depression during maximal exercise was measured 80 ms after the end of QRS with the PR interval as reference level. A positive electrocardiographic response during exercise was defined as horizontal ST depression equal to or greater than 0.1 mV.

The technique for myocardial perfusion imaging has been described.[9] During the same testing session in which the exercise electrocardiogram was performed, thallium-201 (1.5 to 2 mCi) was injected intravenously, 1 minute before maximal exercise. Images (250,000 counts) were obtained in the anterior, left anterior oblique 45° and 65° positions. A separate thallium study at rest was performed 2 to 4 days after the exercise study. The 3 thallium studies (preintervention, 6-week rest and stress) were independently interpreted without computer processing by 2 observers who had no knowledge of the clinical, angiographic or electrocardiographic findings. Each view was separated into 5 segments, yielding a total of 15 segments. The thallium uptake in each segment was classified as: 0 = normal; 1 = possibly reduced; 2 = reduced; and 3 = absent. The maximal defect score 45 originates from 15 segments times a maximal score of 3. The data are presented as the percentage of a maximal defect score (equal to 45 or 100%) that would be obtained if no thallium uptake was shown on the 3 views.

Radionuclide ventriculography during submaximal exercise: Twenty-one patients underwent semisupine bicycle exercise testing with radionuclide ventriculography 17 ± 6 days after AMI while taking their usual medications. The Frank lead system was used for continuous monitoring of the electrocardiographic response to exercise. Exercise commenced at 200 kpm/min and increased by 200 kpm/min at each subsequent exercise level. The patients exercised for 5 minutes at incremental workloads until 1 of the following endpoints was reached: (1) a heart rate of 120 beats/min; (2) complex ventricular arrhythmias; (3) angina pectoris; (4) a decrease in blood pressure during exercise; and (5) exhaustion or dyspnea. Multigated equilibrium blood pool imaging was performed using an in vivo technique of labeling red blood cells with 20 mCi of technetium-99m sodium pertechnetate. Data acquisition was performed in a modified 30° to 60° left anterior oblique view with a 10° caudal tilt adjusted to provide the best definition of the interventricular septum. All images

TABLE I Thallium-201 Data at Rest and During Exercise in the Two Treatment Groups and in Patients with Patent and Occluded Infarct-Related Coronary Artery

	Control (n = 20)	Streptokinase (n = 19)	p Value	Opened (n = 26)	Closed (n = 13)	p Value
Admission thallium-201 scintigraphy defect score (%)	32 ± 18	42 ± 17		38 ± 17	36 ± 21	
Thallium-201 scintigraphy during maximal exercise (5–6 weeks after MI)						
HR at rest (beats/ min)	76 ± 14	77 ± 13		78 ± 13	73 ± 15	
HR at peak exercise	139 ± 20	144 ± 21		144 ± 22	137 ± 17	
Workload (W/min)	149 ± 44	148 ± 43		147 ± 44	151 ± 44	
Abnormal ECG	12 (60%)	8 (42%)		13 (50%)	7 (54%)	
Defect score at rest (%)	22 ± 18	19 ± 13		15 ± 12	31 ± 17	0.002
Defect score during exercise (%)	27 ± 17	30 ± 14		25 ± 13	34 ± 17	
Change in thallium-201 defect score						
Between admission and late study at rest	10 ± 16	23 ± 14	0.01	23 ± 16	5 ± 10	0.001
Between late study at rest and during exercise	5 ± 7	11 ± 6	0.01	10 ± 6	3 ± 7	0.006

ECG = electrocardiogram; HR = heart rate; MI = myocardial infarction.

were acquired using a Elscint Apex-215M gamma camera. Twenty-four synchronized images were acquired in 64 by 64 byte mode for 3 minutes. Data acquisition was begun at each workload after the completion of 2 minutes of exercise, which allowed the heart rate to stabilize. Left ventricular ejection fraction was calculated after determination of background-corrected left ventricular time-activity curve. For each frame in the cardiac cycle, activity within the region of the left ventricle was determined using a second-derivative edge-detection algorithm

Coronary angiography: Angiographic patency was considered present if the infarct-related artery showed a good runoff of contrast material. The interpretation was made by an angiographer unaware of the results of the thallium scintigram. In the SK group, it was defined from the coronary angiogram performed immediately after SK infusion. Within the 6 weeks after AMI a follow-up angiogram was performed in 29 patients (24 of 26 patients who underwent successful reperfusion and in 5 of 13 patients who did not). Multivessel disease was defined as 70% or more narrowing of luminal diameter of at least 2 of the 3 major coronary arteries (left anterior descending, left circumflex and right). Stenosis was measured by calipers in 2 oblique projections.

Statistical analysis: Data are expressed as mean ± standard deviation. Comparison of data between groups was made by unpaired *t* test. A 2-way analysis of variance was performed with 2 grouping factors (coronary patency and number of diseased vessels). The p values presented for this analysis are from tests on the main effects of these 2 factors whereas the interaction was not significant.

Results

Coronary angiography: The 39 patients were retrospectively separated into 2 groups based on the presence or absence of complete obstruction of the infarct-related coronary artery. Baseline angiography revealed that the infarct-related coronary artery was completely obstructed in 18 of 19 patients (95%) receiving SK and in 14 of 20 patients (70%) in the control group. Recanalization of complete coronary artery obstruction occurred in 16 of 18 patients in the SK group and in 3 of 14 patients in the control group. Thus, post-intervention angiography revealed patency of the infarct-related coronary artery in 26 of 39 patients (67%). An anterior infarct was present in 13 of these 26 patients (50%) and in 7 of 13 patients (54%) with coronary obstruction. Twenty of these 26 patients had greater than 70% luminal stenosis of the artery; 5 patients had a 50 to 70% stenosis and 1 patient had a 30% residual stenosis. Follow-up angiography available in 24 of these 26 patients revealed reocclusion in 2 patients with greater than 90% luminal stenosis (2 of 24 [8%]). In 7 of these 24 patients, there was a substantial decrease (10 to 30%) in the remaining stenosis of the infarct-related coronary artery on the follow-up angiogram compared with the acute angiography. These 7 patients had greater than 70% stenosis that decreased to a 50 to 70% stenosis. Twenty-two patients had 1-vessel and 17 patients had multivessel disease, including 10 with 2-vessel and 7 with 3-vessel coronary disease (and no left main coronary artery stenosis).

Enzyme kinetics data: Peak creatine kinase values were lower in patients with incomplete coronary obstruction (1,377 ± 1,087 IU) than in those with complete obstruction recanalized (3,176 ± 1,123 IU) or not recanalized (2,184 ± 1,386 IU). The time required to reach the peak creatine kinase value did not differ significantly between patients with incomplete coronary obstruction on the baseline angiogram (15 ± 4 hours) and those in whom complete obstruction was recanalized (14 ± 6 hours). In both groups the creatine kinase value peaked earlier than in patients in whom complete coronary obstruction was not recanalized (23 ± 5 hours).

Thallium-201 scintigraphy at rest: Thallium-201 defect scores were compared for the preintervention and the 5 to 6 weeks' follow-up studies (Table I and Fig. 1).

Defect score decreased by 10 ± 16% units in the control group and by 23 ± 14% units in the SK group (p = 0.01). The decrease was related to opening of the infarct-related artery (23 ± 16% units in the patients with opened vessel vs 5 ± 10% units in those with closed vessel, p = 0.001).

Thallium-201 scintigraphy during maximal exercise: The results of exercise thallium-201 scintigraphy are listed in Table I. Only 2 patients had chest pain during exercise (the first with patent infarct-related artery and 1-vessel disease; the second with complete obstruction and 3-vessel disease). Positive electrocardiographic findings during exercise were found in 8 patients (42%) treated with SK (6 with 1-vessel disease) and in 13 (50%) with opened infarct-related vessel (7 with 1-vessel disease). The individual changes in thallium-201 defect scores during maximal exercise are shown in Figure 2. The magnitude of thallium defect score reflecting ischemia (exercise-induced score change) was significantly (p = 0.01) larger in patients in the SK group (11 ± 6% units) than in patients in the control group (5 ± 7% units). The exercise-induced defect score was found to be significantly associated with opening of the infarct-related vessel; in the patients with opened vessel, the exercise-induced defect score was 10 ± 6 vs 3 ± 7% units in the patients with closed vessel (p = 0.006). As shown in Table II, this difference was independent of the number of diseased coronary vessels (2-way analysis of variance).

Radionuclide ventriculography during submaximal exercise: Table III and Figure 3 illustrate the magnitude of change in ejection fraction from rest to submaximal exercise in 21 of 39 patients. Comparison of the admission (postintervention) contrast ejection

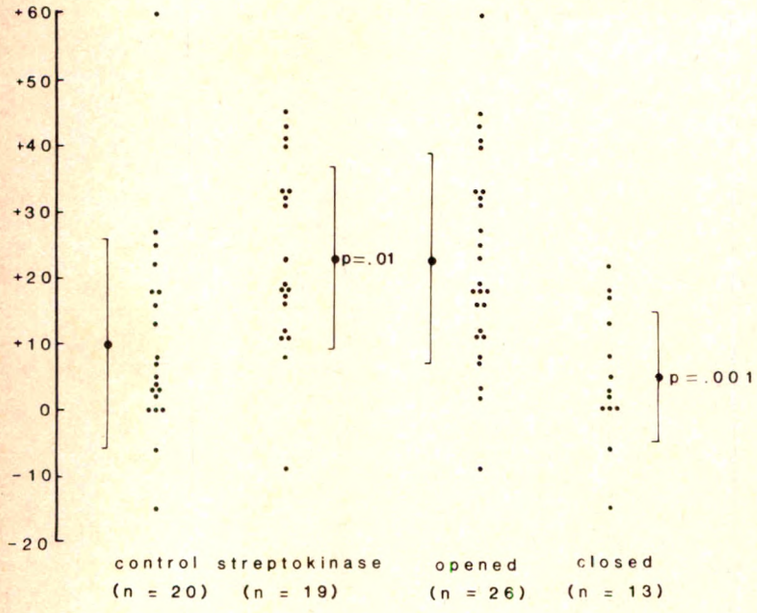

FIGURE 1. Individual changes in thallium-201 defect score at rest between admission and late scintigrams in control and in streptokinase groups as well as in patients with patent and occluded infarct-related coronary artery. Changes in defect score are expressed in percent units and are equal to the admission defect score at rest minus the late score at rest.

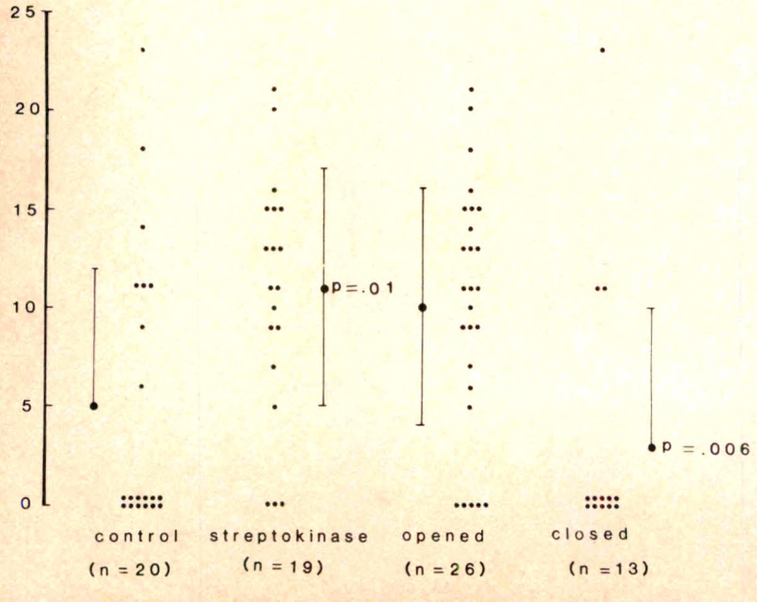

FIGURE 2. Individual changes in thallium-201 defect score during maximal exercise. Changes in defect score are expressed in percent units and are equal to the defect score during exercise minus the defect score at rest.

TABLE II Thallium-201 Data at Rest and During Exercise in Patients Subclassified into 1-Vessel and Multivessel Coronary Artery Disease

	Opened (n = 26)		Closed (n = 13)		p Value	
	1-Vessel Disease (n = 15)	Multivessel Disease (n = 11)	1-Vessel Disease (n = 7)	Multivessel Disease (n = 6)	Opened vs Closed	1 vs Multivessel Disease
Admission thallium-201 scintigraphy defect score (%)	38 ± 18	38 ± 16	44 ± 21	27 ± 19		
Thallium-201 scintigraphy during maximal exercise						
Abnormal ECG	7 (47%)	6 (55%)	1 (14%)	6 (100%)		
Defect score at rest (%)	18 ± 13	12 ± 10	38 ± 16	23 ± 16	0.001	0.03
Defect score during exercise (%)	28 ± 15	22 ± 11	41 ± 18	27 ± 13		0.04
Change in thallium-201 defect score						
Between admission and late study	10 ± 6	10 ± 7	3 ± 9	4 ± 6	0.001	
Between late study at rest and during exercise	20 ± 14	26 ± 18	6 ± 14	4 ± 5	0.007	

ECG = electrocardiogram.

TABLE III Data at Rest and During Exercise in the Two Treatment Groups and in Patients with Patent and Occluded Infarct-Related Coronary Artery. Submaximal Radionuclide Angiographic Data are Included in this Group of 21 Patients

	Control (n = 11)	Streptokinase (n = 10)	p Value	Opened (n = 14)	Closed (n = 7)	p Value
Submaximal RNA Exercise data (2–3 weeks after MI)						
HR at rest (beats/min)	77 ± 12	77 ± 26		75 ± 22	82 ± 13	
HR during exercise	113 ± 15	109 ± 24		108 ± 20	117 ± 16	
Abnormal ECG	2	1		1	2	
LVEF at rest (%)	46 ± 16	45 ± 15		45 ± 16	47 ± 16	
LVEF during exercise (%)	55 ± 18	50 ± 19		49 ± 17	60 ± 20	
Change in LVEF during exercise (%)	9 ± 10	5 ± 7		4 ± 7	13 ± 9	0.03
Admission thallium-201 scintigraphy defect score (%)	35 ± 18	42 ± 17		40 ± 16	35 ± 21	
Thallium-201 scintigraphy during maximal exercise (5–6 weeks after MI)						
HR at rest (beats/min)	74 ± 11	74 ± 13		74 ± 11	73 ± 14	
HR at peak exercise	135 ± 23	144 ± 23		142 ± 26	134 ± 16	
Workload (W/min)	154 ± 44	168 ± 37		158 ± 44	166 ± 34	
Abnormal ECG	5	5		7	3	
Defect score at rest (%)	25 ± 18	14 ± 10		24 ± 14	33 ± 20	
Defect score during exercise (%)	29 ± 19	26 ± 13		14 ± 12	30 ± 16	
Change in thallium-201 defect score						
Between admission and late study at rest	10 ± 12	28 ± 14	0.005	26 ± 13	5 ± 10	0.002
Between late study at rest and during exercise	4 ± 8	12 ± 6	0.03	10 ± 7	3 ± 9	0.07

LVEF = left ventricular ejection fraction; RNA = radionuclide angiography; other abbreviations as in Table I.

fraction and the predischarge radionuclide ejection fraction showed no significant differences between the patients treated with SK (52 ± 12 and 45 ± 15%; difference not significant [NS]) and the control subjects (51 ± 12 and 46 ± 16%; NS). The patients with obstructed artery had an initial ejection fraction of 52 ± 13% and a predischarge ejection fraction of 47 ± 16% (NS). The ejection fraction in patients with incomplete obstruction or reperfused artery was initially 50 ± 11% and at follow-up 45 ± 16%. The 2 groups did not differ significantly with regard to initial or interval change in ejection fraction. The exercise-induced increase in left ventricular ejection fraction was significantly higher in patients with complete coronary obstruction ($p = 0.03$). Among the patients with 1-vessel disease ($n = 13$), the increase in ejection fraction during exercise was also higher in patients with closed infarct-related artery (12 ± 9% units) than in those with opened artery (5 ± 9% units). In the same subgroup of 21 patients, the magnitude of thallium defects reflecting exercise ischemia (change between study at rest and during exercise) was higher in the patients treated with SK ($p = 0.03$) than in the control group, and higher in patients with patent infarct-related artery ($p = 0.07$) than in patients with closed vessel.

Discussion

Five to 6 weeks after AMI, patients treated with SK had improvement in their perfusion scintigrams at rest compared with those at admission, but had more exercise-induced ischemia. In this randomized, angiographically controlled trial of intracoronary SK therapy, the reduction in thallium perfusion defect at rest and the subsequent exercise-induced ischemia occurred in those patients with subtotal occlusion of the infarct-related artery or with successful reperfusion, both in those treated with SK and in the control group.

In this trial, the patients were retrospectively classified on the basis of the angiographic demonstration of patency or total obstruction of the infarct-related artery. Analysis of creatine kinase curves lent further support to the angiographic data; an early peaking of creatine kinase values was found both in patients with catheterization reperfusion and in those with incomplete coronary obstruction on the baseline angiogram. Our population included only the 39 patients who underwent exercise thallium scintigraphy 5 to 6 weeks after AMI. All patients were asymptomatic besides 2 who had angina during exercise. In the remaining 44 patients enrolled in the trial, recurrent coronary events occurred in 19 patients: 1 patient had a reinfarction, 12 underwent coronary balloon angioplasty or bypass surgery and 6 had angina pectoris or abnormal exercise electrocardiographic findings. Those 19 patients represent 70% of those who demonstrated incomplete coronary obstruction or successful reperfusion at the end of admission angiography.

The present study addresses the clinical issue of the residual high-grade stenoses after spontaneous or fibrinolytic reperfusion. Reocclusion has been reported in less than 10 to 32% of patients undergoing follow-up angiography after thrombolysis.[1,2,5,10,11] Of the 26 patients with patent infarct-related coronary artery in the present study, 8% showed reocclusion at the follow-up angiography. Besides the risk of rethrombosis, another potential issue of residual stenosis is exercise-induced ischemia. Previous studies have focused on recurrent angina. In the Western Washington randomized trial, the group treated with SK had less severe angina at the time of hospital discharge than did the control group.[12] In another randomized trial, angina occurred in more control than SK patients during the 19-month follow-up.[13] In a third randomized trial,[14] patients were classified according to the absence or presence of reperfusion after treatment; the incidence of postinfarction angina was similar in the group in whom reperfusion was achieved (21%) and in the group in whom it was not (35%).

In the present study, most patients who underwent thallium scintigraphy during exercise 5 to 6 weeks after

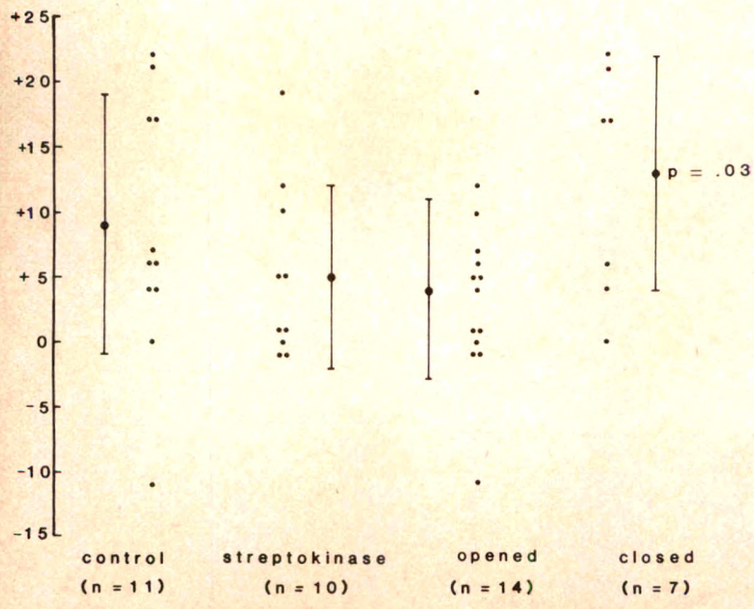

FIGURE 3. Individual changes in radionuclide left ventricular ejection fraction during submaximal exercise.

AMI were asymptomatic. In this group, the presence of an exercise-induced perfusion defect was related to a persistent coronary stenosis. Furthermore, in a subgroup of these patients, radionuclide angiography during submaximal exercise showed that the increase in ejection fraction was significantly greater in patients with closed infarct-related artery (13%) than in those with patent artery (4%). The clinical implications of these findings for the routine management of patients undergoing fibrinolysis after AMI remain to be elucidated. The optimal management course after successful thrombolytic therapy has not been defined. Both percutaneous transluminal coronary angioplasty[15–20] and coronary artery bypass grafting[21–23] have been advocated to prevent reocclusion and recurrent ischemic events. As emphasized by Laffel and Braunwald,[24] these treatments might be indicated after thrombolytic therapy if the patient has angina despite intensive medical therapy or demonstrates persistent myocardial ischemia, particularly in the myocardium perfused by the artery in which thrombolysis has occurred.

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Primary Angiographic Success Rates of Percutaneous Transluminal Coronary Angioplasty

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Three distinct periods in catheter design have been identified since the advent of percutaneous transluminal coronary angioplasty (PTCA) in 1977. In the first period PTCA was performed using a double-lumen balloon catheter that had a fixed, flexible guidewire at the tip. In the second period, an independent, steerable guidewire and the steerable catheter system were used. In the third period, low-profile catheters were introduced. A total of 2,969 patients who had single-vessel PTCA of a native coronary artery was separated into groups according to the period during which PTCA was performed. Introduction of the steerable catheter system was accompanied by improvement in primary success rate in PTCA attempts on the right coronary artery (78% vs 88%, p <0.005). Introduction of the low-profile catheter was accompanied by improved primary success in PTCA attempts on the left anterior descending coronary artery (LAD) (90% vs 94%, p <0.005). The percentage of PTCA attempts on the LAD decreased over the 3 periods (70% to 60% to 56%), while the percentage of attempts on the left circumflex artery increased (7% to 12% to 16%). Before steerable and low-profile catheters were used, there were significant differences in ability to reach and cross stenoses among the 3 major coronary arteries. These differences no longer exist. These results indicate that technical improvements and operator experience have made stenoses in all 3 major coronary arteries equally accessible to dilatation catheters and that primary success rates and reasons for failure in these arteries are now similar.

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Primary success in percutaneous transluminal coronary angioplasty (PTCA) depends on many factors. Patient selection, lesion location, operator experience and equipment choice all play important, but ill-defined, roles.[1–4]

Catheter systems for positioning the angioplasty balloon at the site of stenosis have evolved. Three distinct periods can be identified. In the earliest period, the coronary dilatation catheter was a double-lumen, balloon-tipped catheter with a fixed, flexible guidewire at the distal end, just in front of the balloon.[5] Single, discrete stenoses of the proximal portion of a major coronary artery were the most amenable to successful dilatation.[6]

The second period in coronary dilatation catheters began with the introduction of the independent, steerable guidewire.[7] Torque control and flexibility, superior to the plastic shaft of the original dilatation catheters, permitted the steerable guidewire to be maneuvered into all major coronary arteries and their branches. Once the guidewire was in position the dilatation catheter could be advanced over it. Simultaneous traction on the guidewire and advancement of the steerable dilatation catheter provided improved backup for maneuvering the balloon across a difficult stenosis.[3,8,9]

The most recent period in coronary dilatation catheters began with the introduction of the low-profile catheter. This system preserved the basic design of the independent, steerable guidewire and accompanying catheter. Guidewires for the low-profile system are smaller (0.012 or 0.014 inch vs 0.016 inch), and the balloon tip has a smaller overall dimension.

We undertook this study to determine if changes in the primary angiographic success rate of PTCA at our institution are related to these changes in catheter design.

Methods

Patient selection: From July 14, 1980, to August 15, 1984, 3,716 patients underwent PTCA at Emory University Hospitals. Excluded from this study were 400 patients who underwent multiple-vessel dilatation and 140 patients who had dilatation of a bypass graft. Of the remaining 3,176 patients, 15 had incomplete or ambiguous records. Thus, 3,161 patients who underwent single-vessel dilatation of a native coronary artery formed the population base.

To accurately study changes in primary success rate, we examined the number of native-artery single-vessel PTCA procedures performed and the primary success rates for the

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months after the start of PTCA at our institution. This examination (Fig. 1) revealed an initial steep rise in the primary success rates. To prevent early results from biasing the analysis, we excluded the first 192 patients of our base population or patients whose PTCA procedures were performed before June 1, 1981 (Fig. 1, point A). We therefore restricted the analysis to 2,969 patients undergoing native single vessel PTCA, from June 1, 1981 to August 15, 1984.

Data collection: Since 1980, information on all patients undergoing PTCA at our institution has been collected prospectively. Patient history, physical examination, laboratory studies and PTCA procedure characteristics are recorded on standard forms. After audit for completeness by a research nurse, the data are entered into the cardiac data bank central computer (VAX 11/750, Digital Equipment Corp.).

Angiographic measurements: The angiographic severity of a coronary artery lesion was determined as percent diameter stenosis. Measurement of cineangiograms was done with a programmable digital caliper system (Prodical 1101, A2D Ultrasound, Inc.). In each available projection the frame showing the most severe stenosis in end-diastole was chosen for measurement. The percent diameter stenosis recorded was the mean value of the measurements from 2 or 3 available projections (right anterior oblique, left anterior oblique and lateral). This method has been shown to reduce observer variability.[10]

Lesion length was determined from the same angiographic frames as percent diameter stenosis. Caliper measurements were made of the lesion from the point of first tapering to the point of last widening of the vessel lumen. A calibrated scale allowed translation of measurements into millimeters. The lesion length recorded was the longest of the measurements made in the available projections.

The presence or absence of increased radiodensity within the body of the lesion was noted at the time of cineangiographic review. This result was recorded either as a calcified or noncalcified lesion.

Gradient: Aortic pressure was monitored and recorded from the coronary artery guide catheter. Distal coronary artery pressure was monitored and recorded from the central lumen of the angioplasty balloon catheter. Pressures were determined with tubing filled with saline solution, and strain gauge transducers (Statham P23ID). An automated recording system was used (MEDARRS, Honeywell, Inc.). When the angioplasty balloon catheter was in place at the site of narrowing the difference between aortic and distal coronary artery pressures was monitored and recorded as the transstenotic pressure gradient.

Vessels: The location of a stenosis in 1 major coronary artery or its branches was noted on a coded diagram. For this study all PTCA procedures were grouped according to major coronary artery. A PTCA procedure attempted in a branch of a major coronary artery was therefore grouped by the artery off of which it branched, either left anterior descending (LAD), left circumflex (LC) or right coronary artery.

Success and failure: Primary success in PTCA was defined angiographically as a reduction of at least 20 percentage points in the percent diameter stenosis, determined from measurements of cineangiograms before and after the PTCA procedure. Angiographic success only, rather than clinical and angiographic success, was considered in this study. All unsuccessful PTCA attempts were recorded in 1 of the following mutually exclusive categories: unable-to-reach lesion, unable-to-cross lesion and no-reduction-in-stenosis, meaning that a reduction of less than 20 percentage points in percent diameter stenosis was achieved.

Catheter systems (Fig. 2): From July 1980 through April 1982, PTCA was performed at our institution using a double-lumen balloon catheter (USCI) with a fixed, flexible guidewire at the tip (Fig. 2A). In April 1982 the steerable catheter system (USCI) with an independent, steerable guidewire was introduced (Fig. 2B and C). By May 1982 the steerable catheter was used exclusively for all PTCA procedures. In July 1983 the low-profile catheter (USCI), which maintained the design of the steerable catheter but was smaller in dimension at the balloon tip (Fig. 2D), became available at our institution. The low-profile catheter was used in all cases in which a stenosis was judged too severe to accommodate a standard balloon catheter. It was also used in a catheter exchange whenever a standard balloon catheter could not be passed through a stenosis.

Time periods: The study period from June 1, 1981, to August 15, 1984, was separated into 3 intervals to correspond with the time periods in which the 3 catheter systems were in use: period I (original double-lumen catheter)—June 1, 1981, to April 14, 1982; period II (steerable catheter system)—April

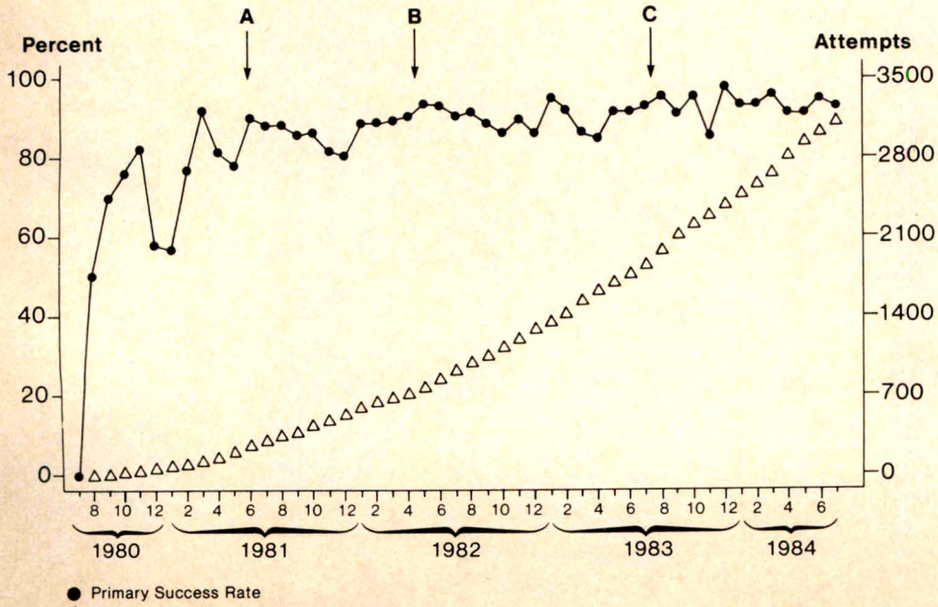

FIGURE 1. Primary success rate in single-vessel percutaneous transluminal coronary angioplasty of a native coronary artery—monthly data. A = end of learning curve; B = introduction of the steerable catheter system; C = introduction of the low-profile catheter.

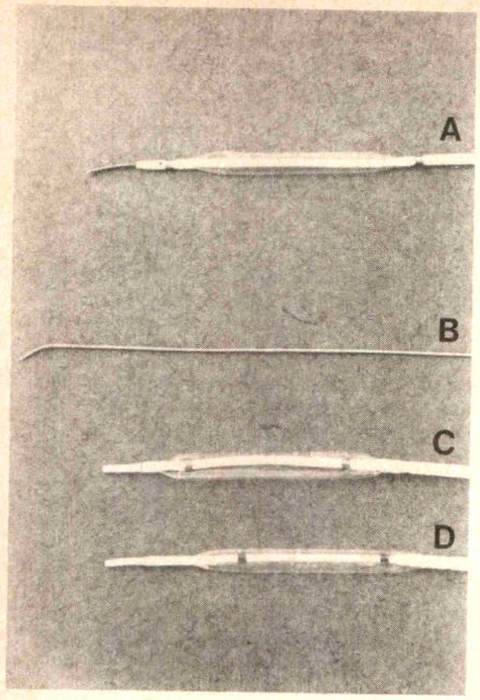

FIGURE 2. A, original fixed guidewire angioplasty catheter. **B,** steerable guidewire. **C,** steerable catheter. **D,** low-profile catheter.

15, 1982 to July 15, 1983; and period III (low-profile catheter)—July 16, 1983, to August 15, 1984.

Statistical analysis: Variables were compared from period I to period II (before and after introduction of the steerable catheter), period II to period III (before and after introduction of the low-profile catheter) and, when appropriate, from period I to period III (earliest experience to most recent experience). Unsuccessful PTCA attempts were compared among the 3 major coronary arteries within each time period. Discrete categorical variables were analyzed with the chi-square test. Continuous variables are shown as mean ± standard deviation and were analyzed with a Student *t* test. A p value <0.05 was considered significant.

Results

The separation of the study period into intervals based upon catheter type resulted in 3 intervals of unequal length and unequal number of PTCA attempts. Period I, from June 1, 1981, through April 14, 1982, consisted of 10.5 months and 499 PTCA attempts (Fig. 1, point B). Period II, from April 15, 1982, through July 15, 1983, consisted of 15 months and 1,137 PTCA attempts (Fig. 1, point C). Period III, from July 16, 1983, through August 15, 1984, consisted of 13 months and 1,333 PTCA attempts.

Proportions (Fig. 3): In each of the 3 periods the proportion of single-vessel PTCA attempts in the 3 major coronary arteries varied. The LAD accounted for the majority in each period, but its percentage of the total fell significantly. The right coronary artery accounted for nearly one fourth of all PTCA attempts in each period, and its share did not change significantly. The LC share of total PTCA attempts increased significantly in each period, from 7% in period I to 12% in period II to 16% in period III.

Success and failure in each time period: The total number of PTCA attempts, number of primary successes, number and category of failures, and their corresponding percentages are shown in Table I.

When the 3 coronary arteries are considered collectively, the primary success rate was 88% (436 of 499 attempts) in period I, 90% (1,021 of 1,137) in period II and 92% (1,233 of 1,333) in period III. The change from the fixed guidewire to the steerable catheter (period I to II) caused a trend toward a decline in the percentage of lesions unable to be reached from 3% to 2%. There was no significant change in the other 2 failure categories. The addition of the low-profile catheter (period II to period III) was accompanied by no change in ability to reach a lesion, but a trend toward declines in both unable-to-cross and no-reduction-in-stenosis to 3% each. The change that occurred between periods I and III was significant ($p < 0.01$). During these same periods, the mean percent diameter stenosis of lesions attempted increased very slightly but significantly. The mean

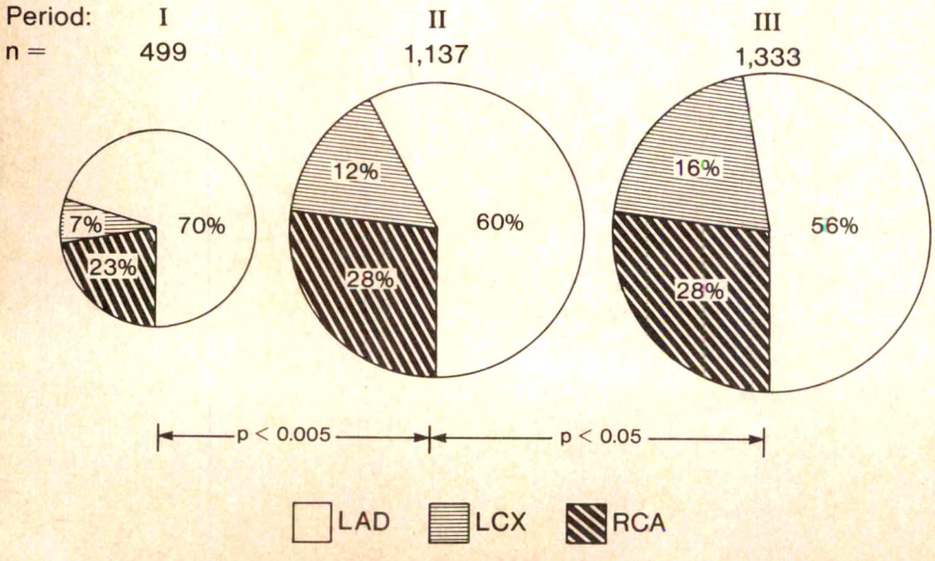

FIGURE 3. Single-vessel percutaneous transluminal coronary angioplasty attempts of a native coronary artery for 3 time periods. LAD = left anterior descending coronary artery; LCX = left circumflex artery; RCA = right coronary artery.

TABLE I Attempts at Percutaneous Transluminal Coronary Angioplasty, Primary Success, and Reason for Failure, All Vessels

	Period I	Period II	Period III
Total attempts	499	1,137	1,333
Primary success	436 (88%)	1,021 (90%)	1,233 (92%)
Unsuccessful			
UTR	17 (3%)	17 (2%)	21 (2%)
UTC	27 (5%)	51 (4.5%)	41 (3%)
NRS	19 (4%)	48 (4.5%)	38 (3%)
	p <0.1	p <0.1	
	p <0.01		
Mean diameter stenosis (%)	73 ± 14	72 ± 13	74 ± 14
		p <0.01	
Mean gradient (mm Hg)	50 ± 16	50 ± 15	51 ± 14
Mean lesion length (mm)	4.9 ± 3.1	6.6 ± 4.3	6.0 ± 3.9
	p <0.005	p <0.005	
	p <0.005		
Calcified	23 (5%)	48 (4%)	80 (6%)

NRS = no reduction in stenosis; UTC = unable to cross lesion; UTR = unable to reach lesion.

TABLE II Attempts at Percutaneous Transluminal Coronary Angioplasty, Primary Success and Reason for Failure, Left Anterior Descending Coronary Artery

	Period I	Period II	Period III
Total attempts	350	678	742
Primary success	315 (90%)	609 (90%)	698 (94%)
Unsuccessful			
UTR	8 (2%)	13 (2%)	7 (1%)
UTC	13 (4%)	22 (3%)	16 (2%)
NRS	14 (4%)	34 (5%)	21 (3%)
	p = NS	p <0.005	
Mean diameter stenosis (%)	71 ± 14	70 ± 13	73 ± 14
		p <0.005	
Mean gradient (mm Hg)	49 ± 15	49 ± 15	49 ± 14
Mean lesion length (mm)	4.7 ± 2.9	6.6 ± 4.3	5.9 ± 3.7
	p <0.005	p <0.005	
	p <0.005		
Calcified	20 (6%)	37 (6%)	63 (9%)
		p <0.005	

NRS = no reduction in stenosis; NS = not significant; UTC = unable to cross lesion; UTR = unable to reach lesion.

TABLE III Attempts at Percutaneous Transluminal Coronary Angioplasty, Primary Success, and Reason for Failure, Left Circumflex Coronary Artery

	Period I	Period II	Period III
Total attempts	34	140	219
Primary succcess	31 (91%)	130 (93%)	195 (89%)
Unsuccessful			
UTR	0	1 (1%)	7 (3%)
UTC	3 (9%)	7 (5%)	8 (4%)
NRS	0	2 (1%)	9 (4%)
	p = NS	p = NS	
	p = NS		
Mean diameter stenosis (%)	76 ± 13	74 ± 13	75 ± 14
Mean gradient (mm Hg)	51 ± 15	53 ± 15	53 ± 14
Mean lesion length (mm)	3.6 ± 2.0	5.6 ± 3.6	5.6 ± 3.6
		p <0.005	
Calcified	0	2 (1%)	2 (1%)

NRS = no reduction in stenosis; NS = not significant; UTC = unable to cross lesion; UTR = unable to reach lesion.

TABLE IV Attempts at Percutaneous Transluminal Coronary Angioplasty, Primary Success and Reason for Failure, Right Coronary Artery

	Period I	Period II	Period III
Total attempts	115	319	372
Primary success	90 (78%)	282 (88%)	340 (91%)
Unsuccessful			
UTR	9 (8%)	3 (1%)	7 (2%)
UTC	11 (10%)	22 (7%)	17 (5%)
NRS	5 (4%)	12 (4%)	8 (2%)
	p <0.005	p = NS	
Mean diameter stenosis (%)	78 ± 14	75 ± 13	77 ± 13
Mean gradient (mm Hg)	52 ± 17	53 ± 15	55 ± 14
Mean lesion length (mm)	5.6 ± 3.8	6.8 ± 4.4	6.5 ± 4.3
	p <0.005		
Calcified (%)	3 (3%)	9 (3%)	15 (4%)

NRS = no reduction in stenosis; NS = not significant; UTC = unable to cross lesion; UTR = unable to reach lesion.

transstenotic pressure gradient and percentage of lesions noted to be calcified did not change. The mean lesion length first increased then decreased, but was higher in period III than in period I.

Success and failure in each vessel: Left anterior descending coronary artery (Table II): The change from the fixed guidewire system to the steerable catheter (period I to period II) was not accompanied by changes in primary success. The mean lesion length was significantly longer in period II than in period I. With use of the low-profile catheter (period III), the primary success rate increased significantly and the failure rates decreased in all 3 categories. Also noted after introduction of the low-profile catheter were increases in mean percent diameter stenosis and the percentage of lesions noted to be calcified. There was a small decline in mean lesion length.

Left circumflex artery (Table III): Neither the introduction of the steerable catheter nor the addition of the low-profile catheter resulted in significant changes in primary success or failure categories. The mean lesion length increased after the introduction of the steerable catheter (period II).

Right coronary artery (Table IV): The introduction of the steerable catheter was accompanied by a significant increase in primary success, with a large decline in the percentage of lesions in the unable-to-reach category and a smaller decline in the percentage in the unable-to-cross category. Use of the steerable catheter was also associated with a significant increase in mean lesion length. The addition of the low-profile catheter was not accompanied by significant changes in primary success or failure categories.

Comparison of vessels within each time period (Table V): In period I (fixed guidewire system), the ability to reach lesions in the 3 major coronary arteries was significantly different (unable-to-reach = 8% for right vs 2% for LAD and none for LC). This difference

TABLE V Comparison of Unsuccessful Attempts at Percutaneous Transluminal Coronary Angioplasty Within Each Time Period

Vessel	Period I	Period II	Period III
	Unable to Reach Lesion		
LAD	2%	2%	1%
LC	0%	1%	3%
RCA	8%	1%	2%
	p <0.01	p = NS	p = NS
	Unable to Cross Lesion		
LAD	4%	3%	2%
LC	9%	5%	4%
RCA	10%	7%	5%
	p <0.05	p <0.05	p = NS
	No Reduction in Stenosis		
LAD	4%	5%	3%
LC	0%	1%	4%
RCA	4%	4%	2%
	p = NS	p = NS	p = NS

LAD = left anterior descending coronary artery; LC = left circumflex artery; NS = not significant; RCA = right coronary artery.

was not apparent after the introduction of the steerable catheter, and the percentage of unable-to-reach lesions for periods II and III was similar for all vessels (Table V). Before the introduction of the low-profile catheter (periods I and II), there was a significant difference among the 3 major coronary arteries in ability to cross a lesion. This difference was not apparent with use of the low-profile catheter (Table V). The no-reduction-in-stenosis category has not been significantly different among the 3 major coronary arteries for any period (Table V).

Discussion

This study demonstrates that the primary angiographic success of PTCA in single vessel lesions of a native coronary artery has increased significantly over 4 years. Angiographic success has increased in conjunction with increases in complexity of lesions attempted. Improvements in primary success and reasons for failure vary among each of the 3 major coronary arteries. Because of technical improvements (the steerable catheter system and the low-profile catheter), PTCA attempts in all 3 coronary arteries now have similar success rates and reasons for failure. This study has dealt only with primary angiographic success; however, acute complications of PTCA have declined during these same periods.[11]

Registry data: The only other large scale compilation of data on PTCA was that of the National Heart, Lung, and Blood Institute PTCA Registry.[12] This registry contains data on single- and multiple-vessel PTCA attempts from September 16, 1977, to September 30, 1982 (3,079 patients).[1] Early data from our institution was included in the registry but we contributed only 190 patients between June 1, 1981, and registry closure to single-vessel PTCA data on October 1, 1981. The registry data thus serves as a useful comparison. A significant proportion of patients in the registry had multiple-vessel PTCA attempts, whereas the present analysis includes only single-vessel attempts.

Learning curve: Our study supports registry data for the presence of a PTCA learning curve.[1,2] Registry data show that primary success increases linearly over the first 250 investigator attempts. However, registry data were being collected at the time the steerable catheter system was introduced (1981 to 1982). Our data show (Fig. 1) that the learning curve effect exists in the early performance of PTCA even when confined to 1 catheter type (in this case the fixed guidewire model). We specifically excluded from our later analysis these early PTCA attempts, which represent the steeply rising portion of the learning curve. The monthly primary success rates after we began our analysis (June 1, 1981) do not exhibit abrupt changes characteristic of a learning curve even at the points where the steerable catheter and the low-profile catheter came into use. However, the proportion of attempts in the 3 major coronary arteries varied between periods. The percentage of PTCA attempts in the LAD fell significantly, while that in the LC increased. This suggests that the "learning curve" changed from a simple success-vs-failure categorization to one of expanded opportunity for attemping angioplasty in the different coronary arteries, particularly the LC.

Steerable catheter system: The advent of the steerable catheter brought about a reduction in the percentage of PTCA failures owing to inability to reach coronary artery lesions. This was entirely a result of improvement in right coronary artery attempts. In addition, the length of coronary artery stenoses attempted increased after introduction of the steerable catheter, with no decline in primary angiographic success. The value of the steerable catheter was anticipated.[2–4,13] The introduction of the steerable catheter was also accompanied by a decline in the percentage of failures owing to inability to cross the coronary artery stenosis, again particularly in LC and right coronary artery lesions (Tables I, II and III). This suggests that the steerable guidewire was superior to the older, fixed guidewire system for crossing lesions even once they were reached. The ability to steer a guidewire into distal branches of the coronary artery before balloon catheter placement may provide the backup needed to cross more difficult lesions.

Low-profile catheter: As would be expected, use of the low-profile catheter brought about a decline in the percentage of failures owing to inability to cross the lesion. Although lesion length declined slightly after introduction of the low-profile catheter, mean lesion length was still longer than in the earliest period. The mean percent diameter stenosis increased slightly but significantly, and it increased most in the LAD, which had the largest increase in primary angiographic success after introduction of the low-profile catheter (Table II).

Inability to reduce the stenosis: Neither the introduction of the steerable catheter nor the addition of the low-profile catheter had an effect on the percentage of failures owing to inability to reduce the stenosis in any of the 3 vessels. The registry data demonstrated a correlation between a decline in inability to dilate and increased mean balloon inflation time and mean maximum number of inflations.[2,4] Other investigators have

suggested that primary success may be improved by these 2 measures.[14] We did not collect these data from our patients.

The constancy of the no-reduction-in-stenosis category in our data may be related to the finding that overall, the percentage of lesions noted to be calcified remained constant across the 3 periods, and the influence of calcified lesions would probably be detected in this category. Calcification of a lesion very likely reflects its age and degree of distensibility. Additionally, the registry has identified lack of lesion calcification as both a univariate and multivariate predictor of success.[4]

Vessel differences: Right coronary artery lesions have consistently had the highest mean percent diameter stenosis, highest mean transstenotic pressure gradient and longest mean lesion length (Table IV). Despite this, primary angiographic success in right coronary artery lesions has improved the most and now almost equals primary success in LAD lesions. In addition, the left circumflex artery has become accessible to dilatation equipment and its proportion of overall PTCA attempts is increasing.

In conclusion, technical changes have occurred in PTCA, which are reflected in improved primary angiographic success. These changes along with operator experience have made stenoses in all 3 major coronary arteries equally accessible and the reasons for dilatation failure similar. This improvement occurred even as more difficult lesions were selected for attempted angioplasty.

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Digital Quantification Eliminates Intraobserver and Interobserver Variability in the Evaluation of Coronary Artery Stenosis

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A leading problem with subjective interpretation of coronary angiography is high intraobserver and interobserver variability. Four experienced angiographers independently determined percent diameter narrowing of 36 stenoses using 3 methods: by subjective analysis of single-frame cine film images (film), by subjective analysis of digitized nonenhanced single-frame images (digital), and by using a semiautomated digital caliper quantification system (Corona). The reproducibility of interpretations was assessed by comparison of estimated intraclass correlation coefficients. Digital and Corona readings correlated well with subjective interpretation of film ($r > 0.85$ for both). In contrast to Corona, the angiographers systematically overestimated the magnitude of stenoses in the intermediate (50 to 75%) range. Corona markedly improved intraobserver ($p < 0.005$) and interobserver ($p < 0.001$) reproducibility. Corona less frequently misclassified individual observations than did film when categories of less than 50%, 50 to 75% and more than 75% diameter stenosis were used (3.7% vs 31.5%, $p < 0.001$). Our results suggest that digitization of a coronary angiogram in a 512 × 512 matrix has no significant adverse effects on the perception and quantification of stenosis by angiographers. Additionally, automatic measurement of coronary stenosis has 2 major advantages: It is accurate compared with a group of experienced angiographers and for the practical purpose of clinical decision-making, it eliminates intraobserver and interobserver variability.

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A leading problem with conventional coronary angiography is that intraobserver and interobserver variability of subjective interpretation of stenosis severity is high.[1–7] Although automated measurement of stenosis by digital processing has the potential to decrease observer variability, 2 important questions must be resolved before such a program is developed. First, transformation of a cineangiographic image to a digitized format carries the risk of loss of resolution, which can cause errors in evaluation of stenosis. Second, there are no data that establish the superiority of automated processing in reducing intraobserver and interobserver variability for the specific task of quantifying percent stenosis. The goals of this study were to determine the effect of digitizing cine film images upon the visual estimation of stenosis severity and to assess the impact of computer-assisted measurement on the reproducibility and accuracy of interpretation.

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Methods

Data base: Single-frame images of 36 coronary stenoses were obtained from 11 patient cineangiograms. Stenoses with 0 to near 100% luminal diameter narrowing were selected. Five stenoses were in the left main artery, 10 were in the left anterior descending artery, 7 were in the left circumflex artery and 14 were in the right coronary artery. No selection was made with regard to the timing of the frame within the cardiac cycle, the projection, film quality, or whether stenoses were discrete, part of a diffusely diseased artery, concentric or eccentric.

Digital images were obtained by viewing each single-frame cine film image with a television camera (RCA 1005 Vidicon), which served as input to an ADAC 4100C digital angiography system. Digital images were acquired in a 512 × 512 pixel matrix format with 256 gray levels of intensity, without magnification, contrast enhancement or filtering.

Image analysis: Quantification of percent diameter stenosis was performed by 4 experienced angiographers using 3 different methods: visual estimation from both cine film (film) and digital images (digital) and digital caliper measurement from digital images. Each angiographer evaluated percent diameter stenosis of all 36 lesions independently on 9 separate occasions, 3 times for each of the 3 methods (total of 1,296 readings). The general region of the coronary artery which included the stenosis to be analyzed was denoted by an arrow on a celluloid overlay. The angiographers received no instructions other than to visually estimate percent diameter

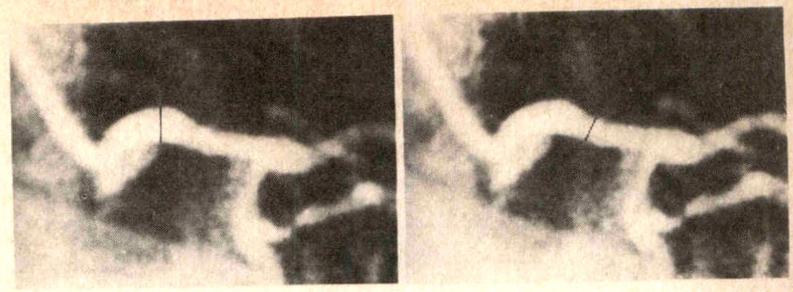

FIGURE 1. Demonstration of Corona. Both panels show the television monitor picture of the same digital coronary image acquired from cine film. The angiographer has placed and adjusted a line segment across what he considers to be the normal artery diameter (**left**) and the maximally stenotic diameter (**right**). Percent diameter stenosis is calculated automatically from the lengths of these segments.

narrowing. Film images were presented on a Vanguard rear projection system. Digital images were viewed on an Ikegame 17-inch black/white monitor. The angiographers were allowed to adjust the light intensity on the film projector and the brightness and contrast controls on the television monitor. Reading sessions were held at least 1 week apart and the sequence of stenoses and the reading format were varied.

For computerized analysis of coronary stenosis, we developed an interactive computer program, which we named Corona (Fig. 1). Corona first magnifies the stenosis region 2 times without changing the gray scale. Using a light pen and keyboard, the angiographer is then prompted to place 2 cursor points across what he considers to be the normal artery diameter and repeats this procedure for the region of maximal coronary narrowing. The length of each diameter segment can be resolved to 1 pixel. Each pixel represented between 0.22 and 0.46 mm, depending on the magnification of the radiographic imaging system. Percent diameter stenosis was calculated as the diameter across the region of maximal narrowing divided by the diameter of the normal segment. Location of the normal and stenotic regions were determined by the angiographer and no additional image processing was permitted.

To assess the accuracy and reproducibility of Corona measurement compared to objects of known dimension, we produced a digital radiographic calibration image of a phantom consisting of 6 drill rods ranging in diameter from 1.02 to 9.92 mm. These rods were positioned with their long axes in a radial arrangement and were imaged at 70 kVp, 300 mA with a 6-ms exposure using a 6-inch image intensifier. All 4 angiographers used Corona on 3 occasions to evaluate the diameter in pixels of each phantom object. No correction for image pincushion distortion was made and no instructions were given regarding where to measure the test objects.

Data analysis: Comparisons for relative accuracy between the 3 methods of quantifying percent stenosis were made by linear regression analysis.[8]

Intraobserver and interobserver reproducibility of each method was quantified by computation of estimated intraclass correlation coefficients. Intraclass correlation coefficients were calculated from a 1-way analysis of variance for repeated measures.[9,10] These coefficients can range from 0 to 1.0 and approaches 1.0 as the agreement between interpretations improves. The intraclass correlation coefficients for intraobserver and interobserver reproducibility for each method were compared using Fisher's Z transformation and chi-square statistics.[11] Throughout the text, pairwise testing between methods (p values) have been adjusted for multiple comparisons.

To assess the potential impact of computerized analysis on clinical decision-making, the frequency with which an individual reading misclassified stenoses was compared for each method. Stenoses were categorized as less than 50%, 50 to 75% and more than 75% diameter narrowing, based on the mean value of the 12 readings determined with each of the 3 methods.

Results

Phantom validation: Corona analysis of the calibration image showed a strong linear correlation between the mean observed diameter vs the true diameter of the 6 test objects [Observed(pixels) = 3.3 × True(mm) + 0.3; r = 0.99]. Thus, each pixel represented 0.3 mm, which was within the range expected in the clinical images. Additionally, the variability of Corona measurements was small; more than 95% of observations were within 1.2 pixels of the mean for each object. Therefore, variability closely approached the spatial resolution of the entire imaging system.

Method comparisons: To establish that the 3 methods exhibited broad agreement as measurement techniques, the mean percent luminal diameter narrowing for all 36 stenoses was determined. For film images the mean (± standard deviation) diameter stenosis was 59.1 ± 22.7%. This was not significantly different from the mean percent stenosis determined by the digital or the Corona methods: 60.8 ± 25.6% and 55.5 ± 21.3%, respectively.

Figure 2 is a comparison of the mean percent stenosis for visual estimation of individual lesions displayed by digital and film methods. These 2 methods showed a strong linear correlation (r = 0.93) and the regression equation (y = −1.0 + 1.0x) did not differ statistically

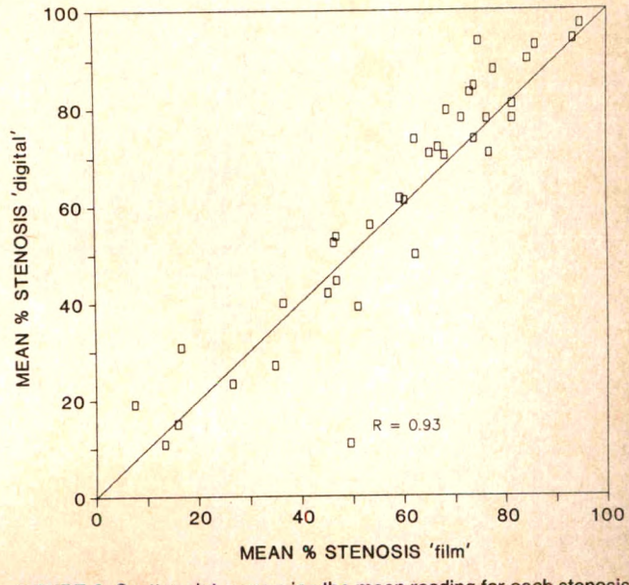

FIGURE 2. Scatter plot comparing the mean reading for each stenosis as estimated from digital images and cine film images.

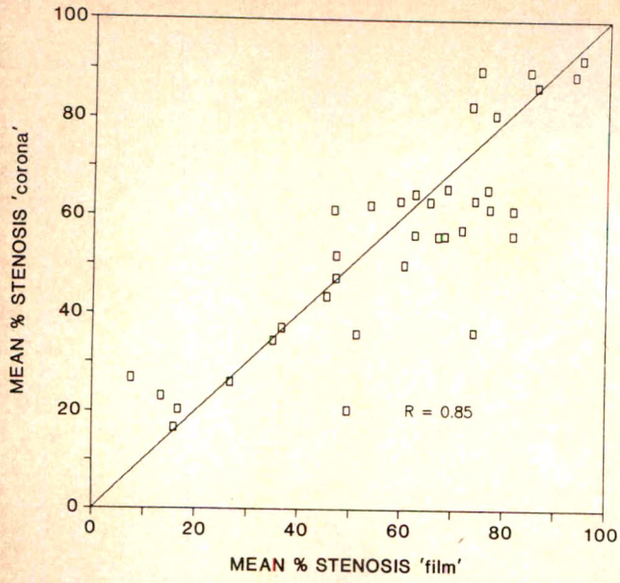

FIGURE 3. Scatter plot comparing the mean reading for each stenosis as measured by Corona with visual estimation from cine film.

from the line of identity. Thus, the accuracy of the interpretation of digital images using conventional film reading as a standard, was high. Agreement between the 2 methods for a given stenosis was good; 97% of stenoses read from digital images agreed with film reading within 18% diameter stenosis. These data suggest that digitization of film images had no systematic effect on the visual estimation of stenosis severity.

Figure 3 shows the comparison of Corona to film reading. Although the correlation coefficient was r = 0.85, the regression line was significantly different from the line of identity ($y = 8.4 + 0.8x$, $p < 0.05$). A systematic difference was found between the 2 methods: stenoses between 50 and 75% by Corona were interpreted to be more severe on film in 12 of 17 instances.

Comparisons between Corona and digital images revealed similar systematic differences ($r = 0.91$, $y = 9.3 + 0.8x$). This latter result suggests that the method of quantification, rather than the process of image digitization, was responsible for the systematic differences.

Reproducibility: Figure 4 demonstrates the spread of all observations, for each method of quantifying stenosis. Variability in the visual estimation of both film and digital images was substantial: the average standard deviation per stenosis were 12.6 and 10.7%, respectively. This variability was greatest between 50 to 75% stenosis. The largest difference in subjective interpretation of an individual stenosis was 0 vs 95%. In comparison, the variability of stenosis measurements using Corona was narrow. The mean standard deviation was 3.8% and variability was evenly distributed for stenoses of all severities.

An example of intraobserver variability is shown in Figure 5. The spread of the 3 interpretations for each of the 36 stenoses by observer 2 is shown for his film and

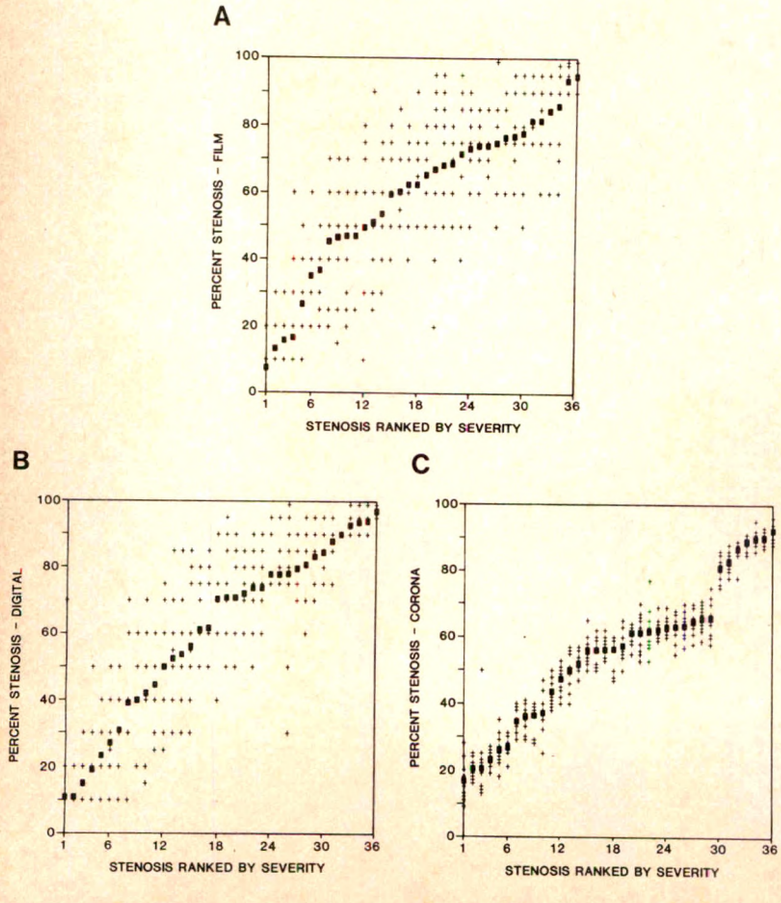

FIGURE 4. Distribution of individual observations (**plus signs**) for each stenosis by film, digital and Corona methods (**A, B** and **C,** respectively). Stenoses are ranked by mean severity. The sum of plus signs per vertical column appears less than 12 where readings coincide.

Corona readings. The results are typical of all 4 observers in 2 respects. First, Corona interpretations displayed much less variability. Second, for subjective film interpretation, variability was greatest for stenoses of moderate severity, whereas with Corona, variability was evenly distributed.

The differences in intraobserver reproducibility, as quantified by intraclass correlation coefficients, are shown in Table I. For each angiographer, the intraclass correlation coefficients for stenoses evaluated by Corona was greater than that for film. Since no significant differences between angiographers were found, we used mean intraobserver intraclass correlation coefficients as a composite index of intraobserver reproducibility. The difference between film and Corona methods was highly significant ($p < 0.005$).

Figure 6 shows the interobserver variability by stenosis from film and Corona readings. The mean of each angiographers 3 readings per stenosis are plotted for each method. For film readings, observer 1 consistently overestimated the severity of stenoses in relation to the other angiographers. Despite the tendency to improve interobserver agreement by comparing angiographer's mean readings, rather than first readings, film readers disagreed on stenosis severity by more than 20% for 25 of the 36 stenoses. In comparison, when the same readers used digital quantification with Corona, they agreed within 10% for all 36 stenoses and there was no systematic differences between individual angiographers. Interobserver reproducibility as assessed by intraclass correlation coefficients was significantly greater for Corona than for film (0.97 vs 0.76, $p < 0.001$).

Clinical classification: To assess the clinical significance of differences in interpretation of the severity of stenosis, each stenosis was categorized as less than 50%, 50 to 75% and more than 75% stenosis, based on its mean value for the same method of interpretation. An individual interpretation was then defined as a misclassification if it did not fall in this category. Figure 7 shows the frequency of misclassification for each method of interpretation. Stenoses were misclassified significantly less often with Corona (3.7%) than with visual estimation from Digital (26.4%) or film (31.5%) images ($p < 0.001$ for both comparisons). This pattern was consistent within each category of stenosis severity.

TABLE I Intraobserver Reproducibility

Observer	1	2	3	4	Mean
Film	0.88	0.79	0.88	0.86	0.85
Corona	0.98	0.96	0.98	0.98	0.98
					$p < 0.005$

Assessment of intraobserver reproducibility by estimated intraclass correlation coefficients. Reproducibility improves as coefficients approach 1.0.

Discussion

A leading problem with coronary angiography is the high intraobserver and interobserver variability of subjective interpretation of stenosis severity. As in our study, Bjork et al[1] reported complete agreement between 4 observers in only 37% of coronary angiographic interpretations, and in 40% of the observations, variability was greater than 20%. This lack of agreement in the subjective interpretation of coronary angiograms has been repeatedly confirmed.[2–6] Poor reproducibility may cloud the relationship of coronary anatomy with

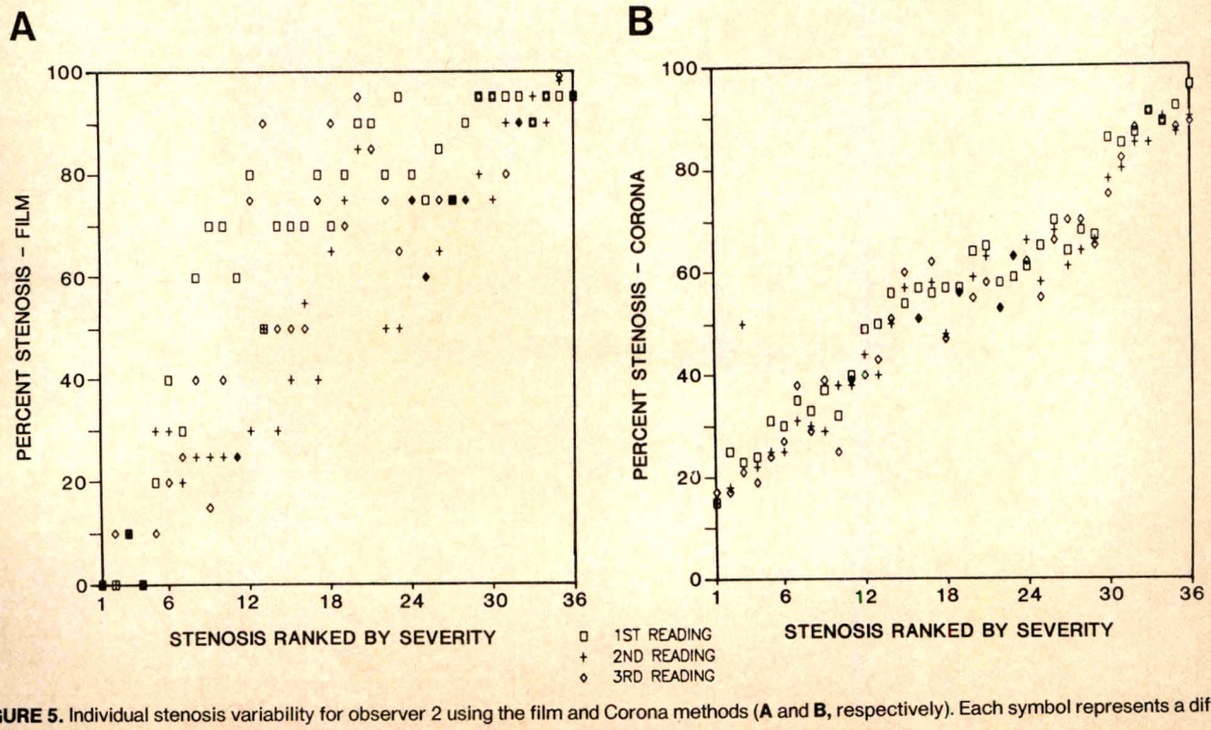

FIGURE 5. Individual stenosis variability for observer 2 using the film and Corona methods (**A** and **B**, respectively). Each symbol represents a different reading.

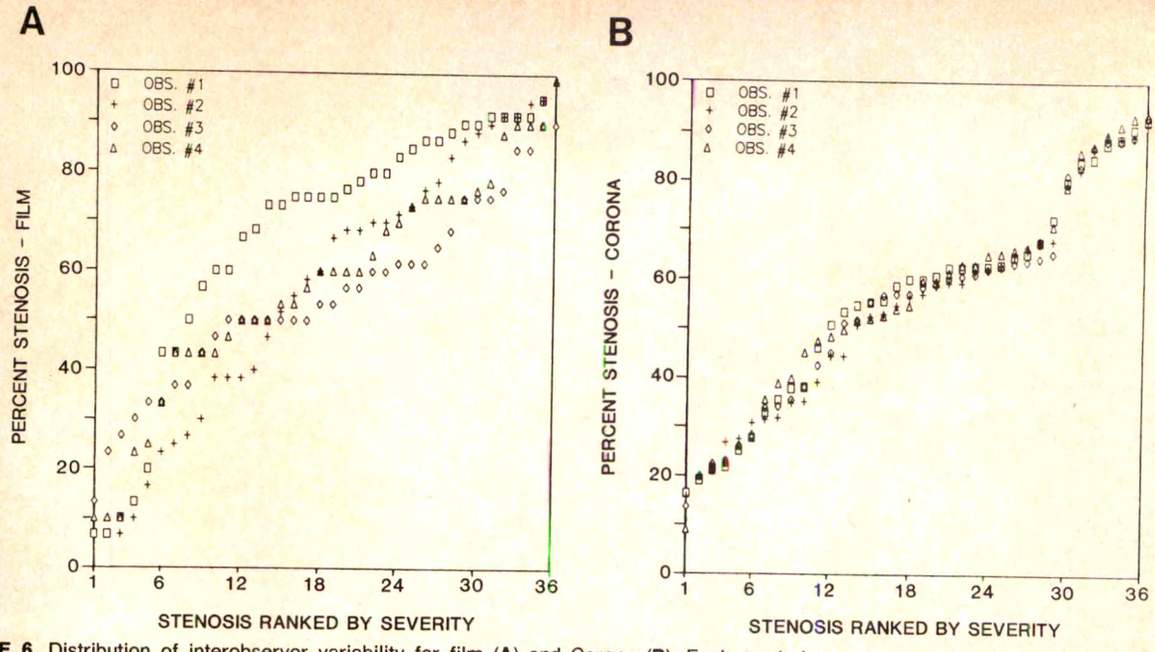

FIGURE 6. Distribution of interobserver variability for film (**A**) and Corona (**B**). Each symbol represents the mean of 3 readings by each observer.

prognosis in important clinical investigations. For example, in the Coronary Artery Surgery Study (CASS), interobserver disagreement between normal and more than 50% diameter narrowing occurred in 15% of the coronary arteries studied.[7] Interobserver reproducibility may be improved by the use of broad categories[12]; however, Galbraith et al[6] found an 18% misclassification rate using the broadest possible categories (greater or less than 50% diameter stenosis).[6] Although a potential solution may be to use consensus readings, Galbraith et al found that when misclassification occurred, the same error was made by at least 2 of the 3 observers in more than 50% of the cases. These data establish the need for a simple, less subjective, more reproducible technique for quantifying coronary stenosis severity.

Digital image processing has the potential to sharply reduce the variability demonstrated in subjective interpretations. However, there are insufficient data establishing that automatic processing increases either the reproducibility or accuracy of interpretation, or that the magnitude of the improvement obtainable would have any importance in clinical practice. Additionally, the procedure has a major theoretical limitation: Compared with the tiny grains of photographic film, an individual digitized picture element is large. There is potential for both loss of image resolution and for measurement errors. Measurement errors can be compounded by expressing coronary diameters as a ratio. One major goal of this study was to determine whether a conventional 512 × 512 digital pixel matrix caused

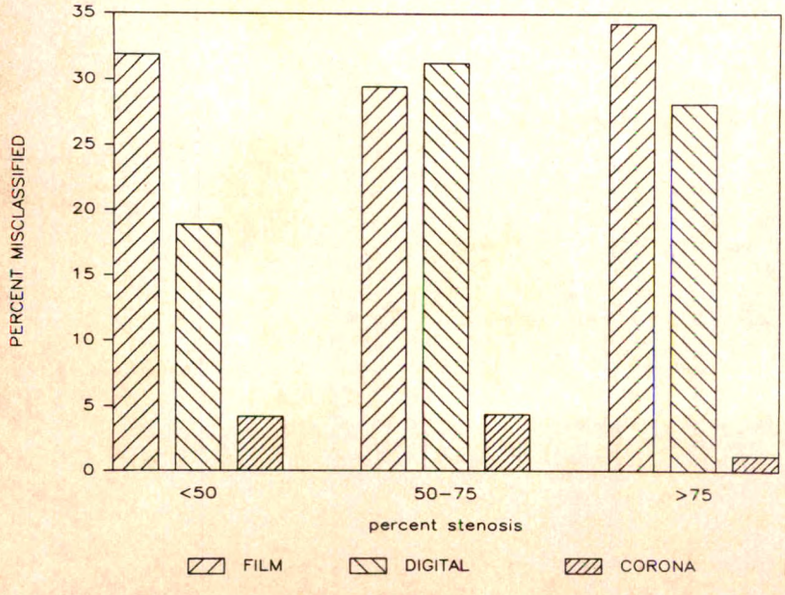

FIGURE 7. Frequency of misclassification by each method. Each stenosis was categorized as less than 50%, 50 to 75% and more than 75% according to the mean of 12 readings for each method. **Bars** represent the frequency with which misclassification of an individual reading occurred for each method. For each category, Corona less often misclassified stenoses in comparison to film or digital methods ($p < 0.01$).

significant loss of image resolution for the specific task of quantifying stenosis.

Effect of digitization on subjective interpretation of stenosis severity: Our data suggest that coronary angiographic images that are digitized in a 512 × 512 pixel matrix are equivalent to cine film for routine clinical use. Direct comparison of film to digital interpretations showed no significant differences. Also, we found that digitization of images before interpretation had no adverse effects on either reproducibility or the rate of clinical misclassification.

The ability of an imaging technique to delineate coronary stenosis depends both on its spatial and contrast resolving powers. Although the spatial resolution of film is 2- to 3-fold greater than a 512 × 512 digital image, its contrast resolution is fixed. Manipulation of television brightness and contrast allows the angiographer additional flexibility. For practical purposes a 512 × 512 pixel matrix appears to be adequate for assessing the severity of coronary stenosis. This is important because higher resolution digital images require more new equipment and software, slow down image acquisition, processing and display rates, and create the need for much larger storage capacity.

Accuracy of digital caliper systems: Computer-assisted quantitation of coronary stenosis was first established by Brown et al[13,14] as both accurate and reproducible in validation studies with x-ray phantoms and postmortem specimens. This method is time consuming and requires cumbersome projection equipment. Scoblionko et al[15] developed an electronic caliper that can be applied directly on projected cine film images and produces measurements of percent diameter stenosis that correlate quite well with the method of Brown et al. Similar to the results of our study, Scoblionko et al[15] found that conventional film reading consistently overestimated stenoses in the 50 to 75% range. Because the actual magnitude of percent diameter stenosis of the arteries in our study were unknown, we can only infer from our phantom data that under controlled conditions, Corona measurements are accurate within 0.3 mm. Absolute measurement of coronary artery diameter is a complex issue because of unresolved anatomic and technical imaging problems. We did not intend in this study to address the accuracy of coronary diameter measurements other than by demonstrating that Corona measurements are comparable to other caliper techniques. In fact, Corona eliminates parallax, improves contrast flexibility, facilitates fine caliper adjustment and ease of caliper placement, which are potential advantages over electronic caliper methods.

Effect of digital processing on reproducibility: Digital caliper quantification of coronary stenosis significantly improved intraobserver and interobserver reproducibility. We confirmed the findings of investigators who showed that subjective interpretation of coronary stenosis severity is highly variable.[1–7] Although intraobserver and interobserver variability for subjective methods were largest for stenoses of moderate severity, with Corona, both intraobserver and interobserver variability were narrow and uniformly distributed, without relation to the severity of stenosis.

Assessment of percent diameter stenosis requires localization of the maximally stenotic segment and the normal region for comparison, perception of the luminal edges, and quantification of these subjective evaluations. Reproducibility may be affected by variability in each of these steps. Digital caliper measurement most certainly reduces quantification error but may additionally improve localization and edge detection variability by forcing the angiographer to evaluate stenoses in a more systematic manner.

Digital quantification made clinical classification more reliable. When we categorized stenoses into the commonly used clinical groupings of less than 50%, 50 to 75% and more than 75% diameter narrowing, 32% of the individual subjective readings of cine film images were misclassified. In contrast, the misclassification frequency using Corona was only 3.7%.

For practical application, digital image processing and quantification was both simple and efficient to use. Once an image is displayed, the entire processes of digitization and quantification takes approximately 30 seconds per stenosis. The information is stored on computer disk and incorporated into a software driven automatic clinical report. Total analysis time per patient is thus comparable to conventional film reading plus report dictation.

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Comparison of Buccal Nitroglycerin and Oral Isosorbide Dinitrate for Nitrate Tolerance in Stable Angina Pectoris

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Sixteen patients with chronic stable angina pectoris were studied to compare the hemodynamic and antianginal effects of buccal nitroglycerin (GTN) in a dose of 3 mg administered 3 times daily and oral isosorbide dinitrate (ISDN) in a dose of 30 mg administered 4 times daily. Compared with placebo, both oral ISDN and buccal GTN treatment induced a decrease in systolic blood pressure at rest over a 5-hour period during acute but not during sustained therapy. Neither buccal GTN nor oral ISDN modified the changes in systolic blood pressure during exercise. Both treatment programs were associated with a higher exercise heart rate during acute therapy. During sustained treatment with buccal GTN, the heart rate during exercise remained greater than that during placebo throughout the 5-hour test period, but during treatment with oral ISDN, only the exercise heart rate at 1 hour was greater than that seen with placebo. Treadmill walking time to the onset of angina and to the development of moderate angina increased significantly during acute therapy with both buccal GTN and oral ISDN. The clinical efficacy of buccal GTN was maintained after 2 weeks of 3-times-daily therapy. In contrast, during 4-times-daily therapy with oral ISDN, treadmill walking time was prolonged for only 1 hour after drug administration. This investigation indicates that tolerance develops during 4-times-daily therapy with oral ISDN, but 3 times daily therapy with buccal GTN is not associated with diminished antianginal effects.

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Isosorbide dinitrate (ISDN) is a useful antianginal agent, but its effects are attenuated during sustained oral therapy.[1,2] Recent studies have shown a similar phenomenon with transdermal ISDN[3] and nitroglycerin (GTN).[4] Reversal of hemodynamic tolerance to oral ISDN has been found after a short washout period,[5] and it has been suggested that intermittent nitrate therapy may be preferable in the management of angina pectoris. Buccal GTN, like sublingual GTN, produces major hemodynamic effects within 60 to 90 seconds of administration[6] and provides protection against angina for as long as the buccal tablet is in place, usually 4 to 6 hours. The present study compares the hemodynamic and antianginal efficacy of buccal GTN and oral ISDN during acute and sustained therapy. The study design permitted assessment of the development of tolerance during therapy with these 2 antianginal agents.

Methods

Sixteen patients (14 men, 2 women), aged 50 to 68 years (average 60.5), with chronic, stable angina pectoris completed this study. Each patient had classic angina pectoris and had a positive treadmill exercise test response, which included the development of angina associated with ischemic ST-segment depression (flat or downsloping ST segments of at least 1 mm for 80 ms after the J point). The diagnosis of coronary artery disease was confirmed by a history of myocardial infarction or by angiographic demonstration of significant coronary artery disease. No patient had cardiomegaly, heart failure, valvular disease, hypertension or heart disease other than coronary artery disease and none was taking digitalis glycosides, β-blocking agents, calcium antagonists or nitrates other than sublingual GTN. Before entering the definitive study, the patients underwent repeated treadmill exercise testing, using the Bruce protocol to familiarize them with the procedure and to determine whether the exercise end point was reproducible. The time to the onset of angina (P_1) was noted and patients were asked to continue exercise until angina was of moderate severity (P_2). During treadmill testing, systolic blood pressure was recorded at the end of each exercise stage and at P_1 and P_2. The CASE Marquette system was used during exercise testing; this system provided data relating to heart rate and ST-segment changes. Over several days, patients exercised on 3 or 4 occasions until the end point (P_2) was reproducible within 90 seconds. Patients whose test results were reproducible and whose total exercise duration was shorter than 9 minutes were considered eligible for this investigation. When reproducibility had been established, exercise testing was carried out 5 minutes after the administration of 0.4 mg sublingual GTN. Patients were considered to be nitrate responders if the time to P_2 was increased by 60 seconds after GTN. Patients entered the definitive investigations when they had reproducible angina pectoris and responded to nitrate therapy.

Definitive investigations (Fig. 1): This was a double-blind, placebo-controlled, crossover study in which patients were assessed during therapy with buccal GTN and oral ISDN. The study was initiated by a 1-week, single-blind period, during which patients received both placebo buccal GTN and placebo oral ISDN. The oral tablets were administered 4 times daily (0700, 1200, 1700 and 2300 hours) and the buccal

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tablet 3 times daily (0700, 1200 and 1700 hours). The buccal tablet was placed against the gum above the upper incisor teeth and patients were instructed not to manipulate this with their tongue or finger. If the tablet dissolved before the next scheduled application, they were told to replace the tablet. At the next scheduled dose, the remaining tablet was removed and a new one was placed. Any residual tablet remaining at 2300 hours was removed. On the seventh day patients came to the laboratory without taking their scheduled morning medications and exercise testing was carried out. Patients then received both placebo medications and exercise testing was carried out after 1, 3 and 5 hours. At 5½ hours, 0.4 mg sublingual GTN was administered and exercise testing was carried out after 5 minutes. Patients took their regularly scheduled medication for the rest of that day.

The next morning exercise testing was carried out and then the patients received their first dose of active medications, either oral ISDN (30 mg) or buccal GTN (3 mg) and the alternate placebo. Exercise testing was carried out after 1, 3 and 5 hours. Patients continued to receive active therapy for 2 weeks. The first 3 days was a titration phase, during which patients received either ISDN, 10 mg 4 times daily, and placebo buccal GTN 3 times daily, or buccal GTN, 1 mg 3 times daily and placebo ISDN 4 times daily. During the next 3 days, the dose of ISDN was increased to 20 mg or the buccal GTN to 2 mg. Patients subsequently received the full dose of either ISDN, 30 mg, or buccal GTN, 3 mg with alternate placebos for a period of 8 days. Thus, all patients received active therapy with either ISDN or buccal GTN for a period of 2 weeks. On day 14, patients came to the laboratory without taking the morning medications and underwent exercise testing. The morning medications were then administered and exercise testing carried out at 1, 3 and 5 hours. At 5½ hours the patient was given 0.4 mg of sublingual GTN and exercise testing carried out 5 minutes later.

After this first active treatment phase, the patient entered another 1-week, single blind, double-placebo period. On the seventh day, exercise testing was carried out. The patients then entered the final 2-week active treatment phase. This was identical to the initial active treatment phase, but the alternate active medications and placebos were administered. Testing was again performed at the time of the initial dose of medication and after 14 days of therapy.

Results

For data analysis, the values at each time period during placebo, ISDN and buccal GTN therapy were corrected for corresponding baseline values (i.e., time 0). To assess the effects on days 1 and 14, comparisons were made with the corresponding placebo day. For the analysis of the treatment effects on days 1 and 14, paired t tests were used. To test for tolerance, the difference between day 1 and day 14 was compared for buccal GTN and oral ISDN.

Rest hemodynamics (Table I): During placebo therapy there were no differences in heart rate and systolic blood pressure at rest during the study period, and the values during the placebo days were comparable. Sublingual GTN treatment produced the expected decrease in systolic blood pressure and increase in heart rate when administered at the end of the study periods ($p < 0.001$). On day 1 buccal GTN significantly lowered systolic blood pressure at rest throughout the study period ($p < 0.05$), but on day 14, the values at rest throughout the study period were not significantly different from placebo values. The heart rate at rest after buccal GTN treatment was higher on day 1, but on day 14 only the value at 3 hours was significantly greater than that during placebo treatment ($p < 0.01$). On day 1, ISDN produced a significant decline in the systolic blood pressure at rest ($p < 0.05$) and an increase in heart rate ($p < 0.05$) throughout the 5-hour study period, but on day 14 the changes were not significantly different from placebo.

Exercise hemodynamics (Table I): The systolic blood pressure and heart rate at the end of exercise were similar during placebo therapy throughout the 5-hour study period, and there were no differences between the placebo days. Neither buccal GTN nor oral ISDN had significant effects on systolic blood pressure during exercise over those seen with placebo. Compared with placebo, the heart rate at the end of exercise during therapy with buccal GTN was greater throughout the study period both on day 1 and day 14. In contrast, however, after ISDN administration on day 1, the heart rate at 1 and 3 hours was significantly greater than placebo ($p < 0.01$), but on day 14, only the heart rate at 1 hour exceeded that during placebo treatment ($p < 0.05$).

Exercise testing (Table II, Fig. 2 and 3): Treadmill walking time was similar during the 5-hour study period

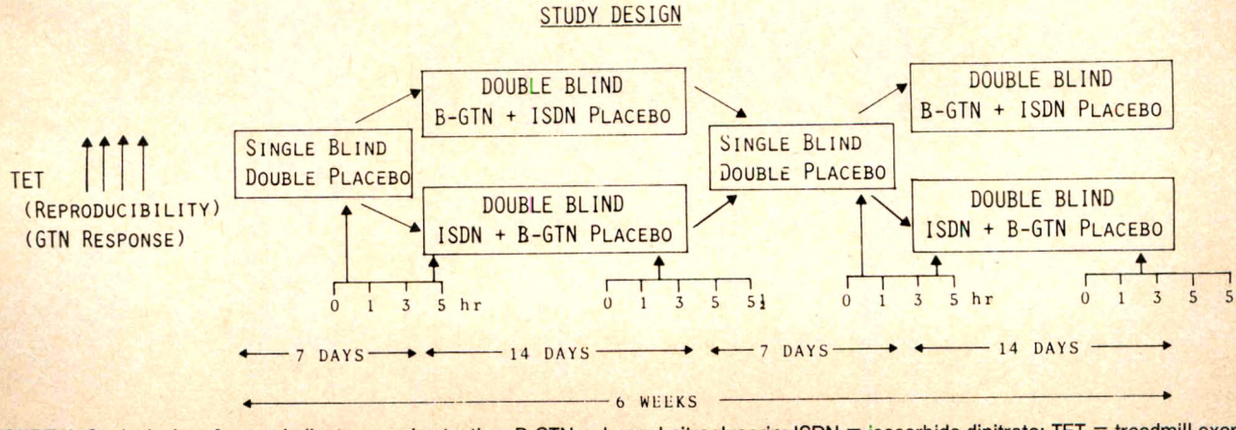

FIGURE 1. Study design. **Arrows** indicate exercise testing. B-GTN = buccal nitroglycerin; ISDN = isosorbide dinitrate; TET = treadmill exercise test.

TABLE I Hemodynamic Data at Rest and During Exercise

	Rest										Exercise (P_2)									
	SBP (mm Hg)					HR (beats/min)					SBP (mm Hg)					HR (beats/min)				
	0 h	1 h	3 h	5 h	GTN_{SL}	0 h	1 h	3 h	5 h	GTN_{SL}	0 h	1 h	3 h	5 h	GTN_{SL}	0 h	1 h	3 h	5 h	GTN_{SL}
Placebo	136	128	131	131	109	75	77	76	77	93	164	163	159	159	162	124	121	121	121	138
	±21	±22	±18	±14	±23	±9	±12	±12	±9	±10	±16	±15	±14	±12	±14	±11	±12	±13	±12	±15
T.GTN-1	135	120	119	121	. . .	76	83	87	86	. . .	160	157	152	154	. . .	119	133	130	131	. . .
	±17	±19*	±18*	±19*	. . .	±12	±8*	±9*	±10*	. . .	±15	±19	±15	±18	. . .	±12	±13*	±13*	±13*	. . .
T.GTN-14	132	123	124	129	110	75	80	85	82	100	161	164	157	163	155	115	126	125	126	141
	±21	±19	±23	±18	±20	±10	±10	±11†	±12	±11	±17	±18	±19	±18	±22	±14	±16*	±14*	±16*	±18
Placebo	132	129	130	128	110	77	78	80	81	95	157	157	158	159	158	117	118	119	118	135
	±20	±15	±16	±15	±18	±10	±10	±12	±13	±14	±19	±17	±17	±15	±18	±14	±16	±15	±16	±15
ISDN-1	129	110	113	116	. . .	77	87	88	88	. . .	159	160	155	149	. . .	118	136	131	128	. . .
	±21	±19*	±19*	±20*	. . .	±9	±10*	±12*	±13*	. . .	±19	±16	±20	±16	. . .	±14	±16†	±15†	±18	. . .
ISDN-14	134	123	124	129	114	75	81	79	81	91	156	155	160	157	160	119	126	123	122	134
	±20	±19	±23	±17	±20	±9	±10	±12	±11	±13	±19	±22	±14	±20	±17	±14	±15*	±15	±16	±17

* Different from placebo ($p < 0.05$); † different from placebo ($p < 0.01$).
Values are mean ± standard deviation.
GTN_{SL} = sublingual nitroglycerin (0.4 mg); h = hour; HR = heart rate; ISDN-1 = first dose of oral isosorbide dinitrate (30 mg); ISDN-14 = dose of ISDN on day 14 (30 mg); P_2 = time to development of angina of moderate severity; SBP = systolic blood pressure (standing); T.GTN-1 = first dose of buccal GTN (3 mg); T.GTN-14 = dose of buccal GTN on day 14 (3 mg).

TABLE II Treadmill Exercise Testing

	TWT (P_1) (seconds)					TWT (P_2) (seconds)					ST (P_2)					Time to 1 mm ST Depression (minutes)				
	0 h	1 h	3 h	5 h	GTN_{SL}	0h	1 h	3 h	5 h	GTN_{SL}	0 h	1 h	3 h	5 h	GTN_{SL}	0 h	1 h	3 h	5 h	GTN_{SL}
Placebo	299	316	292	297	430	381	385	379	378	468	−1.3	−1.3	−1.4	−1.3	−1.4	4.4	4.7	4.8	4.8	6.0
	±111	±122	±111	±109	±125	±111	±118	±118	±119	±107	±0.8	±0.8	±0.9	±0.9	±0.9	±2.3	±2.6	±2.3	±2.4	±2.7
T.GTN-1	298	422	391	366	. . .	372	476	451	437	. . .	−1.3	−1.3	−1.3	−1.3	. . .	4.8	6.1	5.9	5.6	. . .
	±107	±140*	±121*	±153*	. . .	±97	±122†	±114†	±138†	. . .	±1.0	±1.0	±1.0	±0.9	. . .	±2.2	±2.8†	±2.6	±3.0	
T.GTN-14	277	407	364	360	452	364	472	436	428	497	−1.3	−1.3	−1.5	−1.3	−1.3	4.4	6.1	5.4	5.4	6.3
	±86	±116*	±105*	±108*	±90	±89	±101†	±102†	±100†	±83	±1.0	±0.9	±1.0	±1.0	±1.2	±2.2	±3.0†	±2.4	±2.5	±2.8
Placebo	254	279	276	260	428	347	363	364	350	480	−1.2	−1.2	−1.3	−1.3	−1.2	4.4	4.6	4.7	4.3	6.1
	±61	±74	±72	±67	±123	±81	±98	±89	±93	±97	±0.9	±1.0	±1.0	±0.9	±0.9	±2.0	±2.2	±2.1	±2.1	±2.6
ISDN-1	269	443	413	385	. . .	365	528	484	438	. . .	−1.3	−1.2	−1.3	−1.2	. . .	5.0	6.9	6.1	5.9	. . .
	±92	±119†	±128†	±126†	. . .	±111	±106†	±115†	±114†	. . .	±0.8	±0.9	±1.0	±1.0	. . .	±2.7	±3.1*	±2.8*	±2.2	
ISDN-14	287	393	318	309	418	372	458	400	391	471	−1.2	−1.2	−1.3	−1.3	−1.4	4.8	6.3	4.9	4.8	5.8
	±79	±143†	±90	±111	±123	±96	±139†	±110	±116	±122	±1.0	±1.0	±1.0	±1.0	±1.0	±2.5	±3.1*	±2.7	±2.3	±2.8

* Different from placebo ($p < 0.05$); † different from placebo ($p < 0.01$).
ISDN-1 = first dose of isosorbide dinitrate (30 mg); h = hour; ISDN-14 = first dose of isosorbide dinitrate on day 14 (30 mg); P_1 = time to onset of angina; P_2 = time of development of angina of moderate severity; SL = sublingual; T.GTN-1 = first dose of buccal nitroglycerin; T.GTN-14 = dose of buccal nitroglycerin on day 14 (3 mg); TWT = treadmill walking time.

with placebo therapy and no differences were noted between placebo days. In comparison to placebo, time to P_1 and P_2 was significantly prolonged at 1, 3 and 5 hours after buccal GTN on day 1 and day 14 ($p < 0.05$). Oral ISDN produced a marked improvement in exercise time on day 1 for both P_1 and P_2 over 5 hours ($p < 0.01$), and there were no differences from the values with buccal GTN administration. As with buccal GTN, the improvement in walking time was most marked after 1 hour and lesser effects were seen at 3 and 5 hours. In contrast to the improvement on day 1, the response was markedly attenuated during sustained therapy. On day 14, exercise time to P_1 was improved at 1 hour ($p < 0.01$), but the values at 3 and 5 hours were similar to placebo. Similarly, time to P_2 was significantly greater than placebo at 1 hour ($p < 0.05$) and no effect was seen at 3 and 5 hours. The walking time 1 hour after dosing during sustained therapy with ISDN was significantly less than that seen at 1 hour on day 1 ($p < 0.01$).

ST-segment depression at P_2 was similar during placebo therapy and on days 1 and 14 of ISDN and buccal GTN therapy. The time to 1 mm of ST-segment depression was longer at 1 hour on day 1 and day 14 with buccal GTN than with placebo ($p < 0.01$). The time to 1 mm of ST-segment depression was prolonged 1 and 3 hours after oral ISDN on day 1 ($p < 0.05$) and at 1 hour on day 14 ($p < 0.05$).

Discussion

Tolerance to the vascular effects of the nitrates has long been recognized, and in animal studies have shown that the hypotensive effect of organic nitrates is rapidly attenuated during short periods of administration.[7,8] Munition workers exposed to nitrates in their environment often developed vascular headaches, but within a few days these cleared without therapy.[9] Workers soon learned that tolerance disappeared rapidly, and a weekend out of the factory environment was sufficient to lead to severe headaches on return to work. This "Monday headache" signaled the return of normal vascular responsiveness to the organic nitrates. To prevent this loss of tolerance, some workers applied nitrates to their skin during the weekend to prevent such troublesome symptoms.

Although tolerance is recognized, its relevance to the antianginal effects of the organic nitrates is controversial. Danahy and Aronow[10] and Lee et al[11] failed to demonstrate a reduction in the antianginal effects of oral ISDN after 1 to 5 months of therapy with 120 to 160 mg given in 4 divided daily doses. Likewise, Reichek et al[12] failed to show a diminution of antianginal effects during sustained therapy with GTN ointment. Studies from our laboratory have shown that antianginal efficacy is reduced in magnitude and duration during sustained ISDN therapy.[2] Thus, with initial ISDN dosing, walking time was prolonged for up to 8 hours, but when similar doses were administered 4 times daily for 1 week, the improvement in walking time was reduced in magnitude and protection was reduced to 2 hours.[2] These observations have been confirmed in subsequent studies and it is now well established that during short-term, 4-times-daily ISDN therapy, exercise time is not increased beyond 1 to 2 hours after a dose.[13,14]

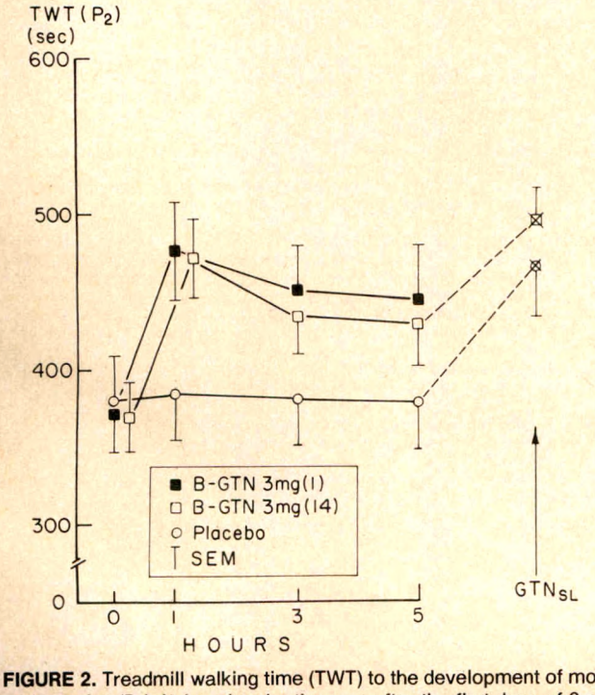

FIGURE 2. Treadmill walking time (TWT) to the development of moderate angina (P_2) during placebo therapy, after the first dose of 3 mg of buccal nitroglycerin (B-GTN 3 mg (1)) and after the same dose on day 14 (B-GTN 3 mg (14)). The response to sublingual GTN (GTN_{SL}) is shown. Values represent mean ± standard error of the mean (SEM). TWT was significantly prolonged over placebo ($p < 0.01$) at each testing time during acute and sustained therapy.

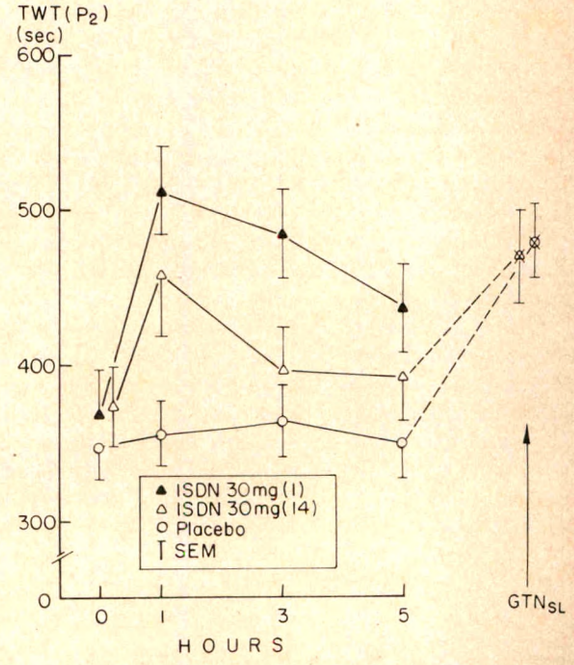

FIGURE 3. Treadmill walking time (TWT) to the development of moderate angina (P_2) during placebo therapy, after the first dose of 30 mg of isosorbide dinitrate (ISDN 30 mg (1)) and after the same dose on day 14 (ISDN 30 mg (14)). The response to sublingual GTN (GTN_{SL}) is shown. Values represent mean ± standard error of the mean (SEM). TWT was significantly prolonged over placebo ($p < 0.01$) at each testing time during acute therapy. During sustained therapy, only the 1-hour value was greater than the placebo value ($p < 0.01$).

The attenuated antianginal effects of ISDN have also been shown in a study with transdermal ISDN.[3] When active ISDN was initially applied, exercise time was prolonged for 8 hours. However, when applied once daily for 7 to 10 days, walking time was similar to that with placebo. Similarly, transdermal GTN patches increased treadmill walking time 2 and 4 hours after the initial application, but during once-daily application for 7 to 10 days, the effects were indistinguishable from placebo therapy.[4] These studies suggest tolerance to the antianginal effects of the nitrates during relatively short periods of regular therapy.

Although nitrate tolerance develops rapidly, there is evidence to suggest that tolerance is also rapidly reversible. We studied the blood pressure response to sublingual ISDN before and during short-term therapy with oral ISDN.[5] Attenuation of the hypotensive effect of sublingual ISDN occurred within 18 hours of initiation of oral ISDN therapy every 6 hours. Similarly, when oral ISDN was replaced with placebo, the normal hypotensive response to sublingual ISDN returned in less than 20 hours. The experimental design did not permit the assessment of the earliest time at which the reversal of this reduced effect occurred. Such rapid reversal of nitrate tolerance suggests that intermittent nitrate therapy might be preferable to the administration schedules that are designed to produce steady-state nitrate levels. Indeed, a recent study with once-daily therapy with sustained release oral ISDN reported no tolerance.[15]

The present study confirmed that 4-times-daily therapy with ISDN is associated with marked attenuation of its effects. Thus, walking time was prolonged for only 1 hour after a dose during sustained therapy. In contrast, buccal GTN administered 3 times daily was not associated with diminished clinical efficacy after 2 weeks of therapy. Is this difference related to differences between ISDN and GTN or to the different dosing schedule? No studies have been directed at the question of attenuated antianginal effects of GTN except for that of Reichek.[12] With GTN ointment in a group of 6 patients, he found no diminution of antianginal efficacy during sustained 3-times-daily application. If the present study had been carried out with similar dosing schedules, attenuated antianginal effects might have been seen with buccal GTN as well as with ISDN. Our current knowledge of the metabolism of the organic nitrates and the biochemical basis for their vasodilatation suggests that ISDN and GTN have similar mechanisms of action. Thus, it is unlikely that tolerance would develop to one of these agents and not the other, except through different dosing schedules.

With increasing evidence that 4-times-daily therapy with ISDN is associated with attenuation of hemodynamic and antianginal effects, dosing intervals must be studied. With the demonstration that relatively short nitrate-free periods are associated with the return of the normal hemodynamic effects of ISDN,[5] one could postulate that 4-times-daily therapy is not appropriate for the management of angina. Thus, perhaps oral nitrates should be given 2 or 3 times daily with a washout period to prevent the development of tolerance. This hypothesis is supported by the recent study from Germany, where once-daily oral therapy with a sustained-release form of ISDN showed no attenuation of antianginal efficacy.[15]

The development of tolerance to the antianginal effects of nitrates during 4-times-daily oral ISDN therapy, with long-acting ISDN cream and transdermal GTN patches raises important questions. Is it desirable to use nitrates in a manner in which therapeutic plasma levels are present throughout a 24-hour period? Apparently, intermittent therapy with a period of nitrate washout may be preferable and may prevent attenuation of the beneficial effects of the organic nitrates.

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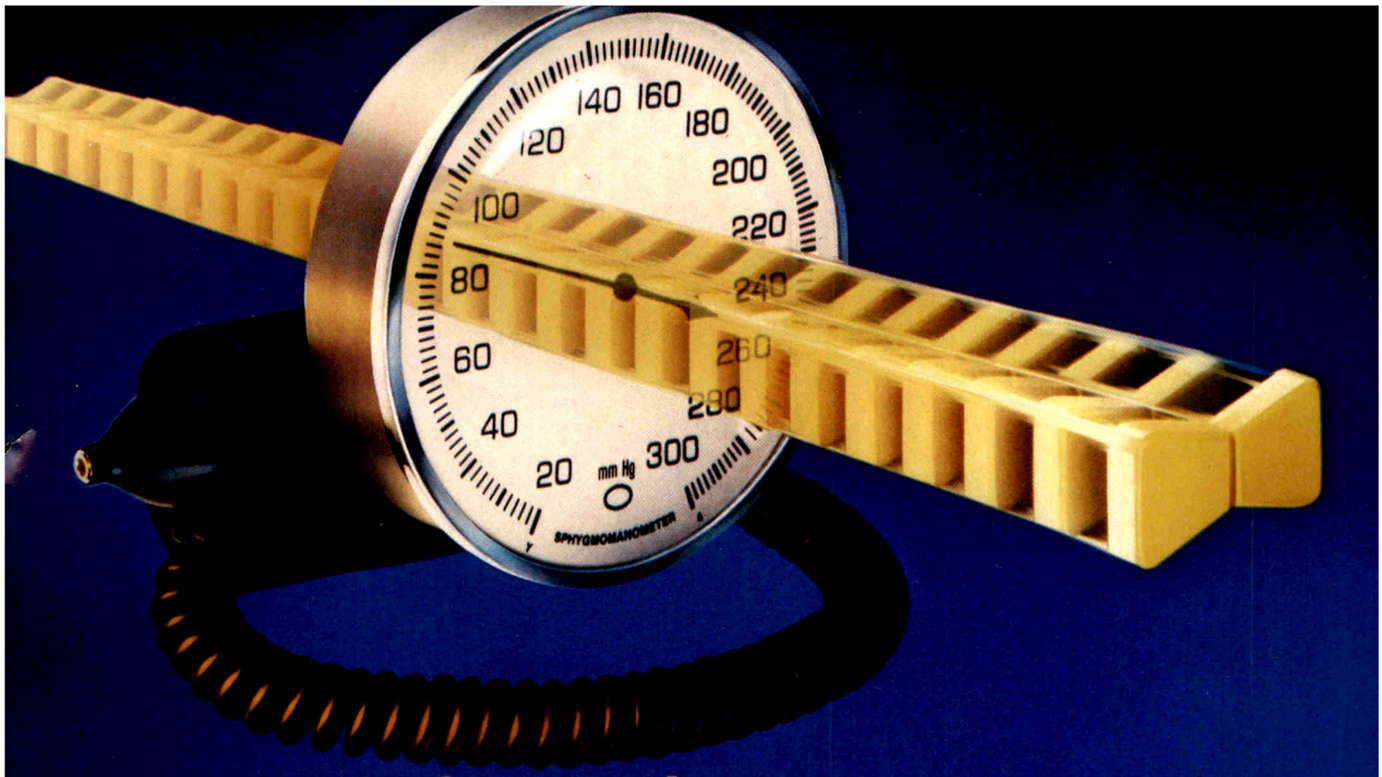

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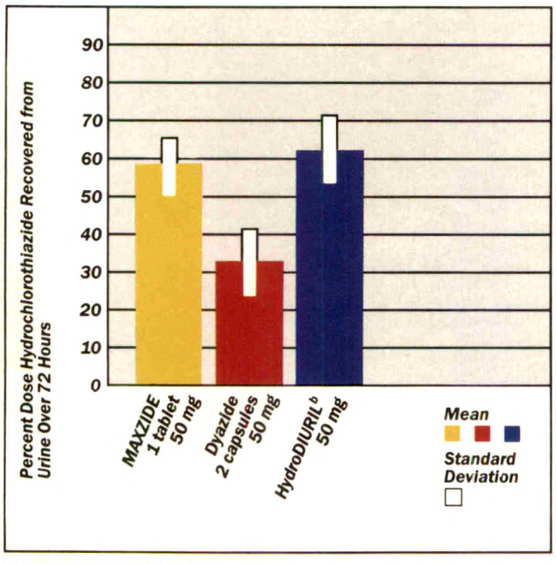
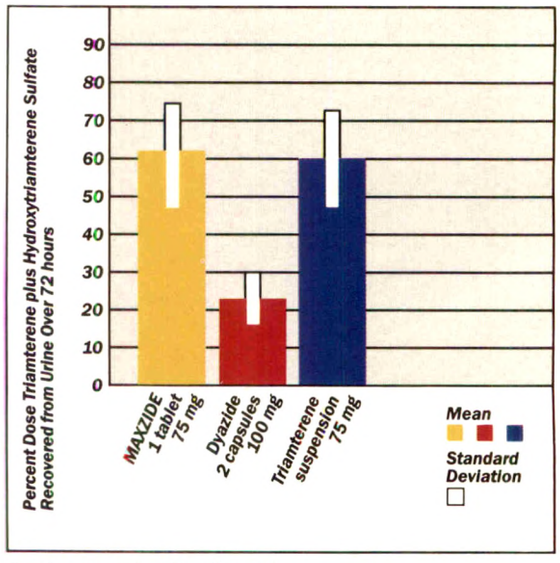
Percent dose of hydrochlorothiazide recovered from urine over 72 hours in subjects[a] given single oral doses



[a]Data from a study of 24 subjects.

[b]HydroDIURIL is the registered trademark of Merck & Co., Inc., for hydrochlorothiazide.

Percent dose of triamterene recovered from urine over 72 hours in subjects[a] given single oral doses



[a]Data from two studies of 24 subjects each.

DELIVERS THE PRESCRIBED DOSE ...
PROVIDES OPTIMAL ABSORPTION OF 75 MG TRIAMTERENE/ 50 MG HYDROCHLOROTHIAZIDE

A CLINICALLY SAFE AND EFFECTIVE ALTERNATIVE IN POTASSIUM-SPARING ANTIHYPERTENSIVE THERAPY

— **FOR PATIENTS ON HYDROCHLOROTHIAZIDE WHO DEVELOP HYPOKALEMIA**
— **FOR NEWLY DIAGNOSED PATIENTS IN WHOM THE DEVELOPMENT OF HYPOKALEMIA CANNOT BE RISKED**
— **FOR PATIENTS TRANSFERRED FROM DYAZIDE**

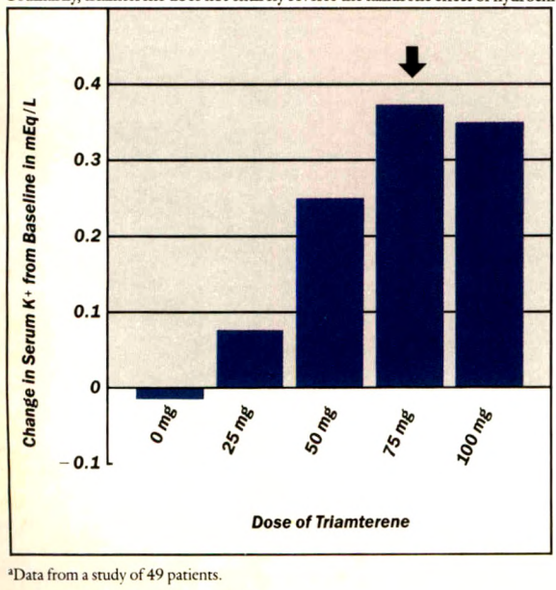
In a transfer safety study, patients taking up to four Dyazide capsules daily were effectively transferred to MAXZIDE q.d. with no compromise in clinical condition.[2]

PROVEN FORMULATION MAXIMIZES POTASSIUM-SPARING EFFECT OF TRIAMTERENE

In a clinical dose-response evaluation, 75 mg triamterene daily most successfully corrected the hypokalemic effect of repeated daily doses of 50 mg hydrochlorothiazide.[3†]

Dose-response evaluation of triamterene's potassium-sparing activity in patients[a] rendered hypokalemic with long-term daily doses of 50 mg hydrochlorothiazide

†Ordinarily, triamterene does not entirely reverse the kaliuretic effect of hydrochlorothiazide.



[a]Data from a study of 49 patients.

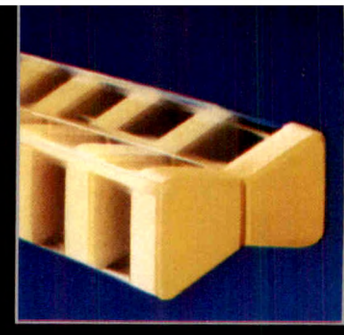
References: 1. Blume CD, Williams RL, Upton RA, et al: Bioequivalency study of a new tablet formulation of triamterene and hydrochlorothiazide. *Am J Med* 1984; 77(5A):59-61. 2. Williams RL, Clark T, Blume CD: Clinical experience with a new combination formulation of triamterene and hydrochlorothiazide (Maxzide) in patients with mild to moderate hypertension. *Am J Med* 1984; 77(5A):62-66. 3. Blume CD, Williams RL: A new antihypertensive agent: MAXZIDE: *Am J Med* 1984; 77(5A):52-58.

*Trademark of SK&F Co., Carolina, P.R.

Please see last page of this advertisement for brief summary of prescribing information.

Once-a-day MAXZIDE™

Triamterene **75 mg**/Hydrochlorothiazide **50 mg**/Lederle



ECONOMICAL, ONCE-A-DAY POTASSIUM-SPARING ANTIHYPERTENSIVE THERAPY

BRIEF SUMMARY

Please see package insert for full prescribing information.

INDICATIONS AND USAGE: *MAXZIDE is indicated for the treatment of hypertension or edema in patients who develop hypokalemia on hydrochlorothiazide alone. It is also indicated for those patients who require a thiazide diuretic and in whom the development of hypokalemia cannot be risked (e.g., patients on digitalis preparations or with a history of cardiac arrhythmias, etc.).* ***This fixed combination drug is not indicated for the initial therapy of edema or hypertension except in individuals in whom the development of hypokalemia cannot be risked.*** *MAXZIDE may be used alone or in combination with other antihypertensive drugs such as beta-blockers. Since MAXZIDE may enhance the actions of these drugs, dosage adjustments may be necessary. Usage in Pregnancy: The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazards. Diuretics do not prevent development of toxemia in pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.*

CONTRAINDICATIONS: *Hyperkalemia: MAXZIDE should not be used in the presence of elevated serum potassium levels (greater than 5.5 mEq/liter). If hyperkalemia develops, this drug should be discontinued and a thiazide alone should be substituted. Concomitant use with other potassium conserving agents such as spironolactone, amiloride HCl or other formulations containing triamterene. Concomitant potassium supplementation in the form of medication, potassium-containing salt substitute or potassium-enriched diets should also not be used. Contraindicated in patients with anuria, acute and chronic renal insufficiency or significant renal impairment. Hypersensitivity to either component separately or other sulfonamide-derived drugs.*

WARNINGS: *Hyperkalemia.*

> *Abnormal elevation of serum potassium levels (greater than or equal to 5.5 mEq/liter) can occur with all potassium conserving agents including MAXZIDE. Hyperkalemia is more likely to occur in patients with renal impairment, diabetes (even without evidence of renal impairment), or elderly or severely ill patients. Since uncorrected hyperkalemia may be fatal, serum potassium levels must be monitored at frequent intervals especially in patients first receiving MAXZIDE, when dosages are changed, or with any illness that may influence renal function.*

If hyperkalemia is suspected, (warning signs include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock) an electrocardiogram (ECG) should be obtained. Monitor serum potassium levels because mild hyperkalemia may not be associated with ECG changes. If hyperkalemia is present, MAXZIDE should be discontinued immediately and a thiazide alone should be substituted. If the serum potassium level exceeds 6.5 mEq/liter, more vigorous therapy is required. The clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose with a rapid acting insulin preparation. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis. The development of hyperkalemia associated with potassium-sparing diuretics is accentuated in the presence of renal impairment (see CONTRAINDICATIONS). Patients with mild renal functional impairment should not receive this drug without frequent and continued monitoring of serum electrolytes. Cumulative drug effects may be observed in patients with impaired renal function. The renal clearances of hydrochlorothiazide, the pharmacologically active metabolite of triamterene, and the sulfate ester of hydroxytriamterene have been shown to be reduced and the plasma levels increased following MAXZIDE administration to elderly patients and patients with impaired renal function. Hyperkalemia has been reported in diabetic patients with the use of potassium conserving agents even in the absence of apparent renal impairment. Avoid MAXZIDE in diabetic patients. If it is employed, serum electrolytes must be frequently monitored. Metabolic or Respiratory Acidosis: Potassium conserving therapy should also be avoided in severely ill patients in whom respiratory or metabolic acidosis may occur, since acidosis may be associated with rapid elevations in serum potassium levels. If MAXZIDE™ triamterene 75mg/hydrochlorothiazide 50mg is employed, frequent evaluations of acid/base balance and serum electrolytes are necessary.

PRECAUTIONS: *Electrolyte Imbalance and BUN Increases: Patients receiving MAXZIDE should be carefully monitored for fluid or electrolyte imbalances, i.e., hyponatremia, hypochloremic alkalosis, hypokalemia and hypomagnesemia. Serum and urine electrolyte determinations should be frequently performed and are especially important when the patient is vomiting or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.*

Any chloride deficit during thiazide therapy is generally mild and usually does not require any specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypokalemia may develop with thiazide therapy, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids, ACTH, amphotericin B or after prolonged thiazide therapy. However, hypokalemia of this type is usually prevented by the triamterene component of MAXZIDE.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

MAXZIDE may produce an elevated blood urea nitrogen level (BUN), creatinine level or both. This is probably not the result of renal toxicity but is secondary to a reversible reduction of the glomerular filtration rate or a depletion of the intravascular fluid volume. Periodic BUN and creatinine determinations should be made especially in elderly patients, patients with suspected or confirmed hepatic disease or renal insufficiencies. If azotemia increases, MAXZIDE should be discontinued.

Hepatic Coma: MAXZIDE should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Renal Stones: Triamterene has been reported in renal stones in association with other calculus components. MAXZIDE should be used with caution in patients with histories of renal lithiasis. Folic Acid Deficiency: Triamterene is a weak folic acid antagonist and may contribute to the appearance of megaloblastosis in instances where folic acid stores are decreased. In such patients, periodic blood evaluations are recommended. Hyperuricemia: Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy. Metabolic and Endocrine Effects: The thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

Insulin requirements in diabetic patients may be increased, decreased or unchanged. Latent diabetes mellitus may become manifest during thiazide administration. Hypersensitivity: Sensitivity reactions to thiazides may occur in patients with or without a history of allergy or bronchial asthma.

Possible exacerbation or activation of systemic lupus erythematosus by thiazides has been reported. Drug Interactions: Thiazides may add to or potentiate the action of other antihypertensive drugs.

The thiazides may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Thiazides have also been shown to increase responsiveness to tubocurarine.

Lithium, when given with diuretics, reduces renal clearance and increases the risk of lithium toxicity. Refer to the package insert for lithium before use of such concomitant therapy.

Acute renal failure has been reported in a few patients receiving indomethacin and other formulations containing triamterene and hydrochlorothiazide. Caution is therefore advised when administering nonsteroidal anti-inflammatory agents with MAXZIDE.

Drug/Laboratory Test Interactions: Triamterene and quinidine have similar fluorescence spectra; thus MAXZIDE may interfere with the measurement of quinidine.

Pregnancy: Category C: The safe use of MAXZIDE in pregnancy has not been established. Animal reproduction studies have not been conducted with MAXZIDE™ triamterene 75mg/hydrochlorothiazide 50mg. It is also not known if MAXZIDE can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, pancreatitis, and possibly other adverse reactions which have occurred in the adult. MAXZIDE should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Thiazides appear in breast milk. If the use of MAXZIDE is deemed essential, the patient should stop nursing. Pediatric Use: The safety and effectiveness of MAXZIDE in children has not been established.

ADVERSE REACTIONS: *Side effects observed in association with the use of MAXZIDE include drowsiness and fatigue, insomnia, muscle cramps and weakness, headache, nausea, appetite disturbance, vomiting, diarrhea, constipation, dizziness, decreased sexual performance, shortness of breath and chest pain, dry mouth, depression and anxiety. These adverse reactions are common to other triamterene and hydrochlorothiazide containing products. Other adverse reactions include:*

Hydrochlorothiazide:

Gastrointestinal: anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. Central Nervous System: vertigo, paresthesias, xanthopsia. Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia, megaloblastosis. Cardiovascular: orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Hypersensitivity: anaphylaxis, purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis. Other: hyperglycemia, glycosuria, hyperuricemia, restlessness, transient blurred vision.

Triamterene:

Hypersensitivity: anaphylaxis, photosensitivity and rash. Other: Triamterene has been reported in renal stones in association with other calculus materials. Triamterene has been associated with blood dyscrasias. Whenever adverse reactions are moderate to severe, therapy should be reduced or withdrawn.

DOSAGE AND ADMINISTRATION: *The recommended dosage of MAXZIDE is one tablet daily with appropriate monitoring of serum potassium levels (see WARNINGS). Patients receiving 50 mg of hydrochlorothiazide who become hypokalemic may be transferred to MAXZIDE directly. In patients requiring 50 mg of hydrochlorothiazide in whom hypokalemia cannot be risked, therapy may be initiated with MAXZIDE. There is no clinical experience with doses exceeding one tablet daily.*

Clinical studies have shown that patients already taking less bioavailable formulations of triamterene and hydrochlorothiazide (totaling 50-100 mg of hydrochlorothiazide and 100-200 mg of triamterene) may be safely changed to one MAXZIDE™ triamterene 75mg/hydrochlorothiazide 50mg tablet per day; these patients should be monitored clinically and with serum potassium after the transfer.

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Collateral Flow in Patients with Acute Myocardial Infarction

WILLIAM D. NITZBERG, MD, HRUDAYA P. NATH, MD, WILLIAM J. ROGERS, MD, WILLIAM P. HOOD, Jr., MD, PATRICK L. WHITLOW, MD, RUSSELL REEVES, MD, and WILLIAM A. BAXLEY, MD

To assess the change in angiographically visualized collaterals in evolving acute myocardial infarction (AMI), coronary arteriograms from 53 patients obtained 6.2 ± 0.2 hours after onset of AMI symptoms were compared with follow-up angiograms obtained 14 ± 1 days later. Collaterals were graded according to intensity score and percent of distal infarct-related artery visualized. Collateral intensity score and the percent of distal infarct vessel visualized by collaterals at baseline were low, and there was a significant increase in both values at follow-up angiography. The group of 20 patients with occluded infarct vessels at follow-up study accounted for these increases. In 33 patients with patent infarct vessels at repeat angiography, collateral intensity score and percent of segment visualized were unchanged. Among the patients with occluded infarct vessels at baseline and subsequent improvement in left ventricular (LV) ejection fraction (EF), baseline collateral score and percent of segment visualized were significantly greater than in patients in whom LVEF did not improve. Thus, in patients with evolving AMI, (1) angiographically visible collaterals are not extensive within the early hours of AMI, (2) the extent of collaterals on follow-up angiography may not be representative of that on the day of AMI, (3) collaterals are considerably more common 2 weeks after AMI, especially in patients with occluded infarct arteries during follow-up, and (4) collaterals present at the time of AMI are associated with improved LVEF at 2 weeks.

(Am J Cardiol 1985;56:729–736)

Coronary artery collaterals are generally believed to be congenitally established channels whose further development and function are promoted by coronary stenosis and myocardial ischemic disease.[1,2] In previous studies collaterals have been examined relative to the circumstances in which they are present in chronic coronary artery disease[3,4] or after an AMI,[5] but only recently have investigators begun to examine their presence and role at the actual time of AMI. The trend toward increased utilization of emergency left-sided cardiac catheterization and coronary angiography, with acute reperfusion interventions such as streptokinase and balloon angioplasty, have provided the opportunity to study these vessels in the acute peri-infarction period.[6–10] The purpose of this study was to assess quantitatively the change in angiographically visualized collaterals in evolving AMI and to assess the relation between collaterals and subsequent improvement in left ventricular (LV) function.

Methods

Patients: Patients had undergone thrombolytic therapy for AMI in a study approved by the human research review committee in January 1982. Consenting patients with no contraindication to thrombolytic therapy or anticoagulation met the following criteria: (1) age 70 years or younger, (2) clinical presentation suggestive of evolving AMI, (3) electrocardiogram showing ST-segment elevation of 1.5 mm or more in 2 or more leads, or marked T-wave changes alone in an otherwise classic clinical presentation, (4) emergency catheterization including coronary angiography, left ventriculography and reperfusion intervention available within 12 hours of onset of pain, and (5) follow-up angiography performed within an average of 2 weeks later to assess patency of the infarct-related vessel and LV function.

Study design: After a brief medical history and physical examination had been obtained and the patient had given informed consent, all patients were premedicated with diphenhydramine, 50 mg intravenously i.v., and methylprednisolone, 1.0 g i.v. A No. 7Fr or 8Fr sidearm valved sheath was inserted into the right or left femoral artery and was sutured into place. Heparin, 5,000 IU i.v., was given. A pigtail ventriculography catheter was inserted, baseline LV pressure was recorded, and biplane left ventriculography was performed in the 20° cranial–60° left anterior oblique/45° right anterior oblique projections using 45 ml of diatrizoate sodium and diatrizoate meglumine (Renografin-76®) that was power-injected over 3 seconds.

Coronary arteriography of the suspected non–infarct-related artery was then performed, followed by injections in the infarct-related artery. Contrast was injected with enough force and quantity to give good visualization of the major coronary arteries and their tributaries. No specific attempt was made to opacify collaterals, which usually appeared late on the fluoroscopic screen, most often after cessation of contrast injection. Multiple views of the coronary arteries were routinely obtained: right coronary artery—left lateral, 60° left anterior oblique/15° cranial, and 30° right anterior oblique;

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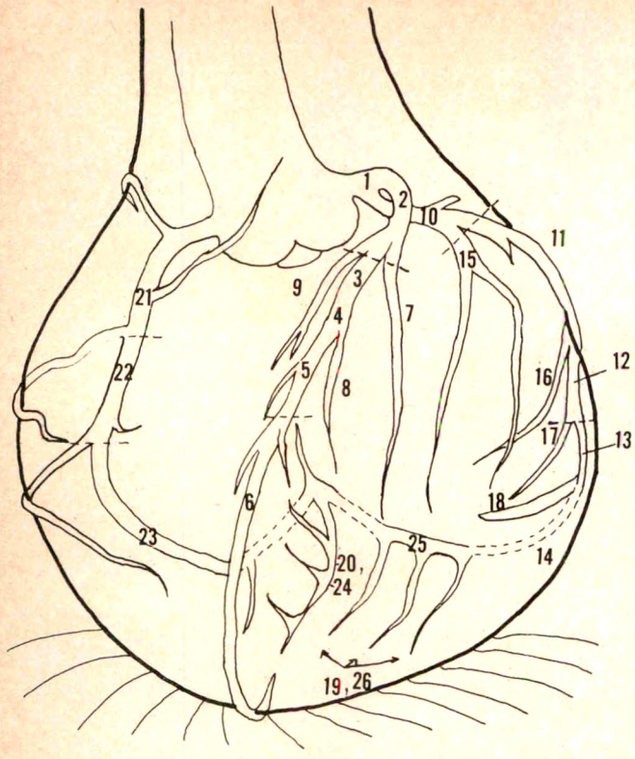

FIGURE 1. Left anterior oblique representation of the infarct related coronary artery segments (modified from the Coronary Artery Surgery Study, Circulation 1981;63:suppl I:I-59, with permission of American Heart Association).

left coronary artery—60° left anterior oblique/15° cranial, left lateral, 30° right anterior oblique, 30° right anterior oblique/15° caudal, and 30° right anterior oblique/15° cranial. Angiograms were recorded on 35-mm film using a Phillips Polydiagnost-C movable C-arm, and were filmed in standard 6-inch mode. If total occlusion or high-grade stenosis of the infarct-related artery was found, the patient received 1 or more interventions, including intracoronary or intravenous streptokinase, with or without subsequent emergency percutaneous transluminal coronary angioplasty. No patient had emergency coronary artery bypass grafting. The details of reperfusion interventions and subsequent management are given elsewhere.[8] The diagnosis of myocardial infarction was confirmed by typical rise and fall of serial CK-MB isoenzyme levels. Left-sided cardiac catheterization with coronary and LV angiography was repeated in a similar fashion an average of 2 weeks later.

Coronary angiograms were viewed on a Tagarno 35 CX cine film analyzer. Coronary angiograms were reviewed by a cardiac radiologist. The baseline and follow-up angiograms were viewed in sequence, without prior knowledge of LV function. Angiographic global LV ejection fraction (EF) was derived by another uninvolved observer according to techniques previously described.[11]

Angiographic criteria for collaterals were direct visualization of accessory blood vesels either filling the distal segment of an occluded or severely stenotic artery or subserving the area of myocardium that would ordinarily be supplied by the severely stenotic vessel (intracoronary collaterals), or visualization of a coronary artery after injection of contrast material into the contralateral vessel (intercoronary collaterals).[2,12] Collaterals were graded according to the percent of distal infarct-related artery visualized by collaterals and by intensity.

The percent of distal infarct-related artery visualized by collaterals was determined in a semiquantitative fashion. Coronary artery segments were identified and categorized according to a modification of the nomenclature used in the Coronary Artery Surgery Study (CASS).[13] Figure 1 shows how the coronary arteries were separated into segments. When vessels or segments thereof were opacified on the cardiac silhouette on cine film, they were identified and quantitated visually based on comparison with CASS coronary artery segments as they would appear in similar roentgenographic projections. A schematic representation of this method is shown in Figure 2. Except for 25% and 75%, values were given to the nearest 10%.

Collateral intensity was scored from 0 to 4: grade 0 = no observed collateral opacification of the distal vessel; grade 1 = faint (questionable) opacification seen in only 1 angiographic projection; grade 2 = mild but definite opacification seen in 2 or more angiographic projections; grade 3 = moderate opacification readily observed but not equal in density to antegrade opacification; and grade 4 = rich opacification,

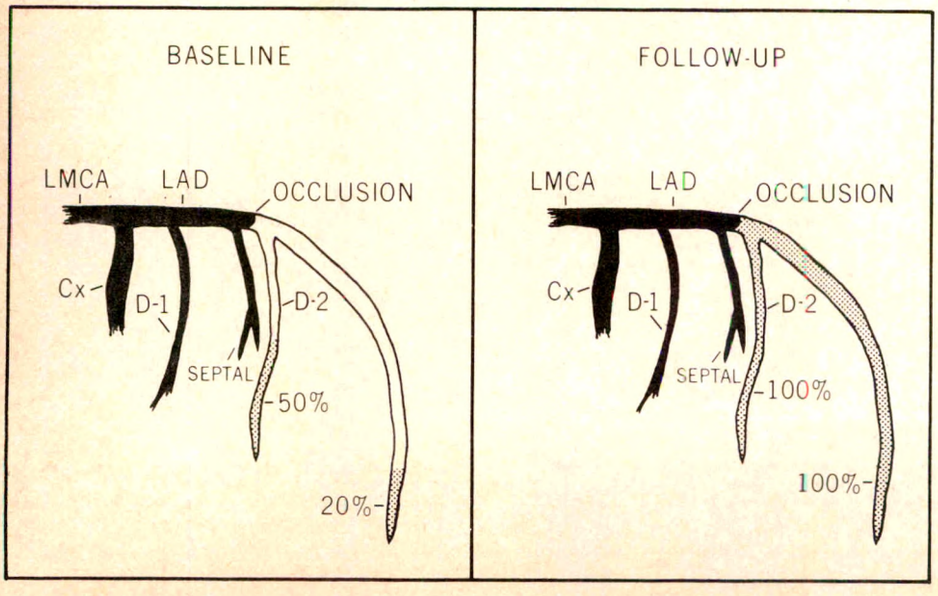

FIGURE 2. How the percent of infarct-related artery supplied by collaterals was determined. **Left,** initial angiogram reveals occlusion of the distal left anterior descending coronary artery (LAD). Twenty percent of the distal LAD and 50% of the second diagonal branch, (D-2) are opacified by collaterals. **Right,** at follow-up angiography, with persistent occlusion of the LAD, the entire distal LAD and the second diagonal branch are opacified by collaterals. Cx = left circumflex artery; LMCA = left main coronary artery.

equal to that which could be seen by anterograde flow. Figure 3 shows an example of intracoronary collaterals to the distal right coronary artery and its tributaries in 1 study patient on initial and repeat angiography.

Statistics: Data are reported as mean ± standard error of the mean. A paired or unpaired t test was used to assess the significance of difference between continuous variables. The chi-square test with Yates' continuity correction was used to assess the significance of differences between noncontinuous variables. The 2-sample Wilcoxon test was used for EF analysis.

Results

Patients: Fifty-three patients with AMI were admitted within 12 hours of onset of symptoms and satisfied the study criteria. Emergency coronary and LV angiography were performed within an average of 6 hours after onset of symptoms. All patients survived to follow-up angiography, which was performed an average of 14 days later. Patients were placed into 2 subgroups for analysis of data. Group 1 included 20 patients whose infarct-related artery was occluded at follow-up angiography. Group 2 included 33 patients whose infarct-related artery was patent at follow-up angiography. Baseline clinical and angiographic characteristics of the 2 groups were similar (Table I).

The mean age of the patients was 52 years on admission; most patients were men. Twelve patients in group 1 and 16 patients in group 2 had a history of angina (difference not significant [NS]). Five patients had a prior myocardial infarction (documented in 4 patients and undocumented in 1 patient), and all of these were in group 1 ($p < 0.01$). No patient had undergone prior coronary bypass surgery. There was a preponderance of 2-vessel coronary artery disease in group 1 and 1-vessel disease in group 2. The infarct-related artery was totally occluded at initial angiography in 87% (46 of 53) of the patients, and the 2 groups did not differ in this regard. No patient had a preintervention stenosis of less than 90% in the infarct-related artery at initial angiography. Of the 20 patients in group 1, 2 (10%) had subtotal and 18 (90%) had total occlusions at initial angiography. Of the 33 patients in group 2, 5 (15%) had subtotal and 28 (85%) had total occlusion at initial angiography. The infarct-related artery was usually the left anterior descending or right coronary artery. Hemodynamic measurements, including LV global EF and aortic and LV pressures, were similar between the 2 patient groups at both baseline and follow-up angiography. The interval from onset of symptoms to completion of initial angiography averaged 6.6 ± 0.5 hours in group 1 and 5.9 ± 0.2 hours in group 2 (NS).

Sixty-six percent (35 of 53) of patients had a successful reperfusion intervention, defined as restoration of patency to an initially occluded vessel, or a decrease in the initial stenosis in a subtotally occluded vessel. Successful reperfusion was seen in 8 patients in group 1 (40%) and 27 patients in group 2 (82%) ($p < 0.002$). Two patients in group 2 and none in group 1 had emergency percutaneous transluminal coronary angioplasty. All patients had CK-MB isoenzyme evidence of AMI.

The interval between initial and follow-up angiography averaged 16 ± 2 days (range 9 to 47) for group 1 patients and 13 ± 1 days (range 3 to 31) for group 2.

Presence of collaterals: Of the 53 patients in this study, 30 (57%) had angiographically visible collaterals at the initial catheterization during their evolving AMI. Of the 46 patients who initially had a totally occluded infarct-related artery, 26 (60%) had visible collaterals. Of the 7 patients with a subtotal occlusion at initial angiography, 4 (57%) had visible collaterals. Despite their presence, in many cases the extent of distal infarct-related vessel opacified by collaterals and the collateral intensity score were unimpressive.

Of the 20 patients in group 1, 12 (60%) had visible collaterals at baseline study, including the 2 patients with subtotal occlusions in their infarct-related artery. Eighteen patients (90%), including the 2 with initial subtotal occlusions, had an increase in extent or intensity of collaterals at the time of follow-up study. One patient had a decrease and 1 had no change in collaterals between the 2 studies. All 20 patients had some visible collaterals at follow-up angiography.

Of the 33 patients in group 2, 18 (55%) had some visible collaterals at initial angiography. These included 16 of the 28 patients (57%) who had completely occluded infarct-related arteries at baseline and 2 of the 5 patients (40%) whose infarct-related arteries were subto-

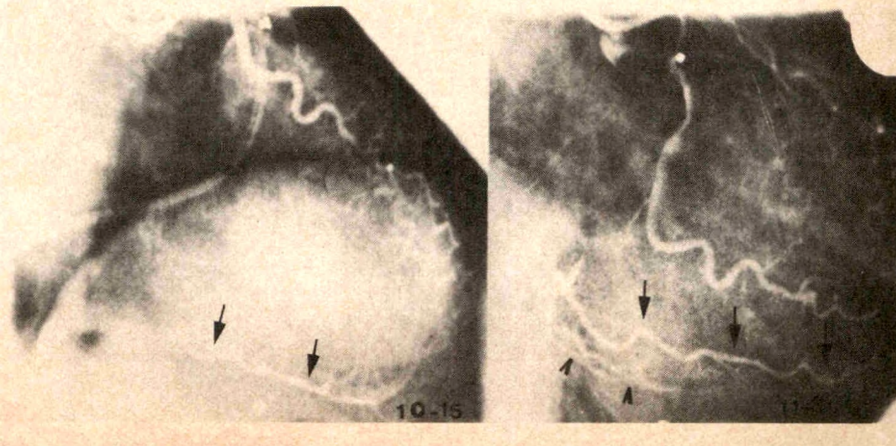

FIGURE 3. Left, right anterior oblique view of a left coronary arteriogram from the initial study of a patient with a right coronary artery occlusion. The **arrows** point to the posterior descending artery seen by intercoronary collaterals and graded with an intensity of 4. **Right,** at follow-up angiography 2 weeks later, the same view now shows, in addition to the posterior descending artery, the posterolateral segment artery, marked by **arrowheads** and also grade 4. The distal right coronary artery can also be seen just proximal to the origins of these branches and is graded as having an intensity of 3.

TABLE I Baseline Clinical and Angiographic Data

Variable	Infarct Artery Occluded at Follow-Up (n = 20)	Infarct Artery Patent at Follow-Up (n = 33)	p Value
Age (yr)	54 ± 2 (37–68)	51 ± 2 (33–70)	NS
Sex	15M/5F	29M/4F	NS
Prior angina	12 (60%)	16 (48%)	NS
Prior AMI	5 (25%)*	0	<0.01
Prior CABG	0	0	NS
Infarct related artery			
Totally occluded at baseline	18 (90%)	28 (85%)	NS
LAD	9 (45%)	16 (48%)	NS
LCx	4 (20%)	2 (6%)	NS
Right	7 (35%)	15 (45%)	NS
Extent of CAD (≥70% stenosis)			
1 vessel	7 (35%)	21 (64%)	
2 vessel	12 (60%)	8 (24%)	<0.05
3 vessel	1 (5%)	4 (12%)	
Aortic pressure (mm Hg)			
Systolic	137 ± 5	136 ± 4	NS
Diastolic	85 ± 3	86 ± 2	NS
LV pressure (mm Hg)			
Systolic	137 ± 4	134 ± 14	NS
Diastolic	23 ± 2	23 ± 1	NS
Global LVEF (%)	50 ± 2 (31–65)	46 ± 2 (27–69)†	NS
Successful intervention	8 (40%)	27 (82%)	<0.002
Emergency PTCA	0	2 (6%)	NA
Emergency CABG	0	0	NA
Interval from symptom onset to completion of angiography (hr)	6.6 ± 0.5 (4–12)	5.9 ± 0.2 (3.7–10)	NS
Interval from initial to repeat angiography (days)	16 ± 2 (9–47)	13 ± 1 (3–31)	NS

* Four documented, 1 undocumented.

† EF data not available for 3 patients in group 2.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; EF = ejection fraction; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricular; NA = not applicable; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

tally occluded at baseline. In 1 of these latter 2 patients collateral intensity slightly increased and in 1 collaterals had disappeared by the time of repeat angiography. Of the 16 patients with collaterals and occluded infarct-related arteries at baseline, 13 (81%) had a decrease in extent or intensity of collaterals, 12 of whom had no visible collaterals, by the time of follow-up angiography. Of the remaining 3 patients, collateral extent and intensity were unchanged in 1 patient and increased in 2 patients between the 2 studies. These latter 2 patients were the only group 2 patients to have nearly total (99%) occlusions in their infarct-related artery at the time of follow-up angiography.

Quantitation of collaterals: *Collateral intensity score:* Figure 4 is a comparison of the mean collateral intensity score at baseline and follow-up angiography for the entire study group (n = 53) and for groups 1 (n = 20) and 2 (n = 33). The mean collateral intensity score for all patients was 0.5 ± 0.1 (range 0 to 4.0). This increased to 0.9 ± 0.2 (range 0 to 4.0) at follow-up angiography. Thus, overall, the mean collateral intensity score increased 0.5 ± 0.2 ($p < 0.02$). For group 1, the mean collateral intensity score was 0.6 ± 0.2 (range 0 to 4.0) at baseline and 2.2 ± 0.3 (range 0 to 4.0) at follow-up, or an increase of 1.6 ± 0.3 ($p < 0.0001$). For group 2 the mean collateral intensity score was 0.4 ± 0.8 (range 0 to 4.0) at baseline and 0.2 ± 0.1 (range 0 to 4.0) at follow-up, a decrease of 0.2 ± 0.8 (NS).

Percent of distal infarct-related artery visualized: Figure 5 is a comparison of the mean percent of distal infarct-related artery visualized at baseline and follow-up angiography. The mean percent of distal infarct-related artery visualized was 16 ± 4% (range 0 to 100%) for all patients at baseline study. This increased to 27 ± 5% (range 0 to 100%) at follow-up angiography, yielding a net increase of 12 ± 5% ($p < 0.04$). For group 1, the mean percent of distal infarct-related artery visualized was 20 ± 7% (range 0 to 100%) at initial angiography and 65 ± 7% (range 20 to 100%) at follow-up angiography, an increase of 45 ± 9% ($p < 0.0001$). For group 2, the mean percent of distal infarct-related artery visualized changed from 13 ± 4% (range 0 to 100) to 5 ± 3% (range 0 to 100) between the 2 angiographic studies, a decrease of 8 ± 4% ($p < 0.03$).

Relation between collaterals and left ventricular ejection fraction: LVEF data were not available for 3

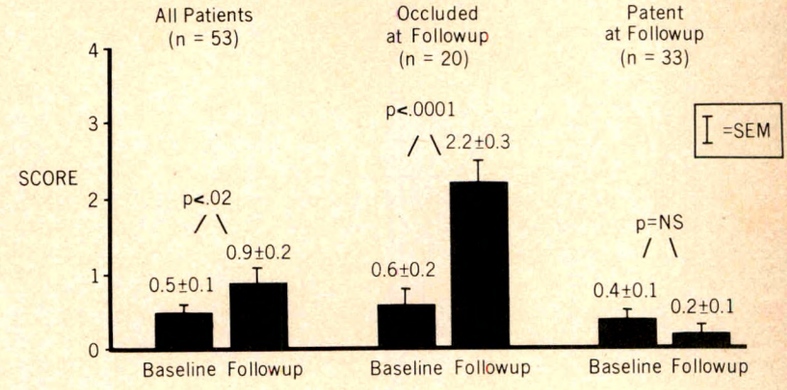

FIGURE 4. Comparison of the mean collateral intensity score at baseline and follow-up angiography for all 53 patients and for the 20 patients with occluded and the 33 patients with patent infarct-related arteries at repeat angiography. NS = not significant; SEM = standard error of the mean.

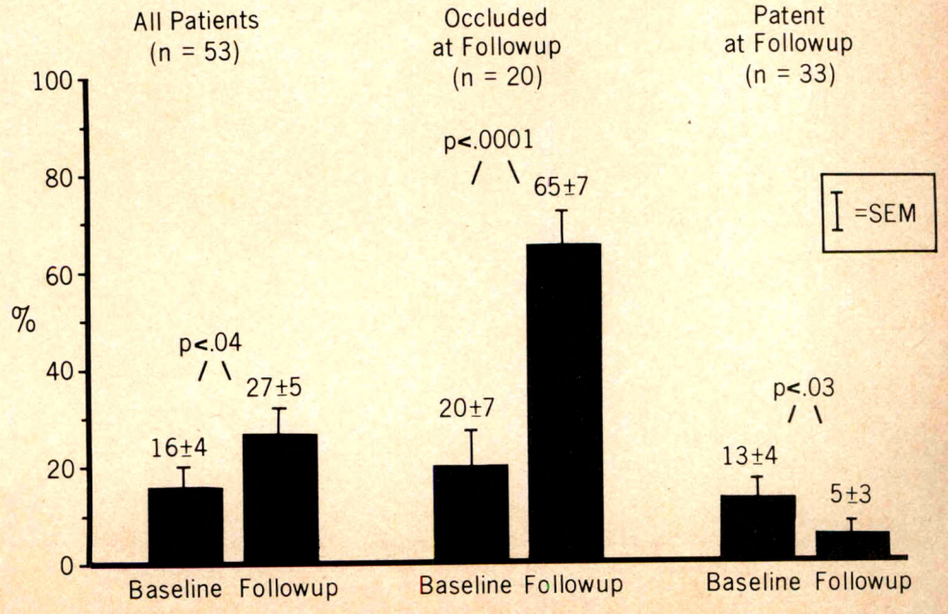

FIGURE 5. Comparison of the mean percent of distal infarct-related artery opacified at baseline and follow-up angiography for all 53 patients and for the 20 patients with occluded and the 33 patients with patent infarct-related arteries at repeat angiography. SEM = standard error of the mean.

patients in group 2 at initial angiography, but were available for all patients at follow-up. The mean global LVEF at baseline angiography was 50 ± 2% (range 31 to 65%) in group 1 and 46 ± 2% (range 27 to 69%) in group 2 (NS). The LVEF at follow-up angiography was 45 ± 2% (range 26 to 63) in group 1 and 49 ± 2% (range 29 to 70%) in group 2 (NS).

We observed a relation between the extent of collaterals present at baseline angiography and change in LVEF in the interval between initial and repeat angiography. In 46 patients the infarct-related vessels were totally occluded at baseline. LVEF data were available for 43 of these patients. In 15 of these patients LVEF subsequently increased (mean 10 ± 1%, range 1 to 19%), and in 28 it decreased or remained the same (mean −8 ± 1%, range 0 to 22%). Figure 6 is a comparison of the mean collateral intensity scores and the mean percent of distal infarct-related artery visualized at baseline angiography for each of these groups. At the time of initial angiography during AMI, the group whose LVEF subsequently increased had a higher mean collateral intensity score (0.8 ± 0.3, range 0 to 4.0) and mean percent of distal infarct-related artery visualized (32 ± 10%, range 0 to 100%) than did those whose LVEF subsequently failed to improve (0.2 ± 0.1, range 0 to 2.0), (7 ± 3%, range 0 to 80%). These differences in mean collateral intensity score and mean percent of distal infarct-related artery visualized were significant at the at the $p < 0.06$ and $p < 0.02$ levels, respectively.

Discussion

Several well-documented coronary collateral pathways are present in humans.[14] Coronary angiography can visualize collaterals of 100 μ or more and usually visualizes only epicardial vessels.[15] Humans have collaterals less than 100 μ in size, and most human collaterals are intramural or subendocardial.[1] Thus, the extent of collateral flow may not be represented by angiographic studies. However, collaterals may be inferred to be present by visualization of an obstructed coronary artery after contrast injection into a nonoccluded vessel or into the same, more proximally obstructed vessel, with no visible communication between the 2. For the purposes of this study, collaterals were considered present if they were visualized or if a portion of distal infarct-related artery was visualized.

The amount of contrast medium injected and duration of the cine run can affect the extent of collaterals seen, especially if contrast is injected specifically to view collaterals. In our study, contrast was injected with sufficient force and duration to opacify the major coronary arteries and their branches, then the cine run was continued until collaterals were well opacified or until it was clear that no collaterals were going to appear. No specific attempt was made to opacify collaterals by injecting with more force. Collaterals usually appeared later on the cine film, frequently at the very end of or after completion of contrast injection. Therefore, it is unlikely that any systematic bias toward better visualization of collaterals was introduced by the amount and rate of contrast injection. Although these factors may have affected collateral visualization, they should have done so in a uniform manner, and the trends in collateral formation and regression are unlikely to be an artifact of the contrast injection technique.

In this study 53 patients with AMI had coronary and LV angiography within a short time after onset of symptoms, and again an average of 2 weeks later. Fifty-seven percent of patients had angiographically visible collaterals to the infarct-related vessel at the time of AMI, and collaterals were seen with equal frequency in patients with total or subtotal occlusions as the cause of their AMI. This is a significantly higher percentage of patients than was reported in smaller series by Schwartz, Schuler and colleagues[9,10] of patients undergoing emergency coronary angiography during AMI, although these investigators did not recognize lower grades of collateral filling. The percentage with

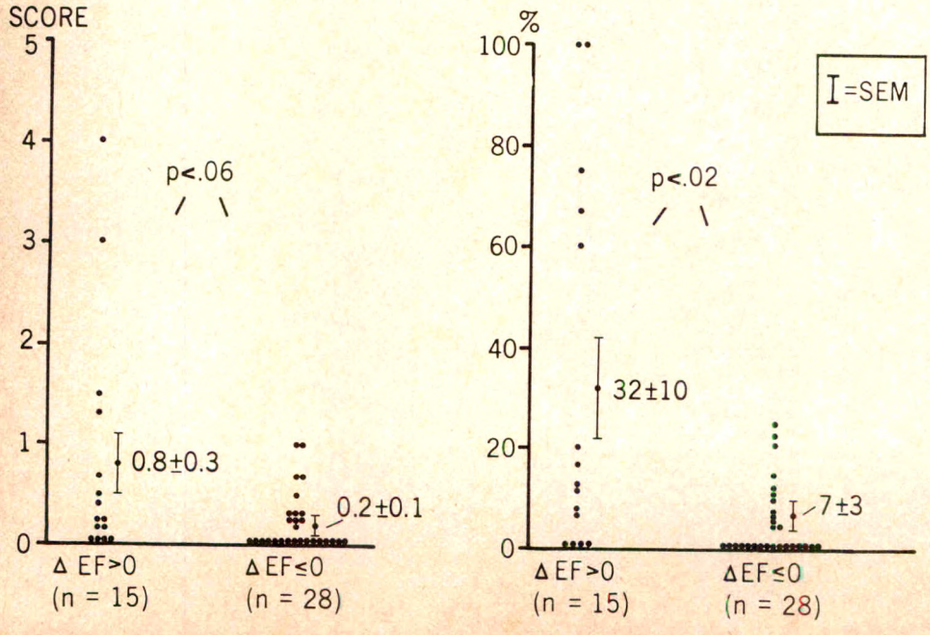

FIGURE 6. Comparison of the mean collateral intensity score (**left**) and the mean percent of distal infarct-related artery visualized by collaterals (**right**) at baseline angiography for the 15 patients in whom left ventricular ejection fraction (EF) improved (**left bar** in each graph) and for the group of 28 patients whose EF failed to improve (**right bar** in each graph) from baseline to follow-up angiography. SEM = standard error of the mean.

baseline collaterals in our study is similar to the figures reported by Rentrop et al.[6,7] In the more recent study by Rentrop's group, however, collateral status to the infarct zone is reported for only 46 of 55 patients who had both baseline and follow-up angiography, and this represented only one-fourth of all the patients in their series who initially had emergency coronary arteriography and were treated by streptokinase infusion.

In this study the extent and intensity of collaterals at baseline during AMI were generally low. The patency status at follow-up angiography had no relation to the degree of initial collateralization. The patency status at initial angiography had no bearing on the degree of collateralization at follow-up study. Rather, it was the presence of occlusion or high-grade stenosis at follow-up that was associated with improvement in the degree of collateralization by that time. Thus, collateral extent and intensity increased in patients whose infarct-related artery was occluded (group 1) or had very high grade stenosis (2 patients in group 2) 2 weeks after AMI.

The presence of increased collateral blood supply 2 weeks after AMI in patients with totally or subtotally occluded infarct-related vessels gives no information about when the increase occurred, nor does it explain what stimulated the increase. It is generally accepted that coronary collaterals are congenitally determined potential channels that do not function except in response to a pressure difference across or between coronary arteries as a result of obstruction or to myocardial ischemia per se,[16,17] or possibly other metabolic alterations.[7] When stimulated, collateral vessels develop thicker, more muscular walls and can function more like arterioles.[18] Experimental studies in dogs show that collateral channels develop over time to a point where they can be rapidly recruited to function maximally or not at all in response to transstenotic pressure gradients and tangential wall stress.[19,20] Similarly, studies in humans have shown the rapid appearance and regression of functioning collaterals after coronary artery bypass grafting and graft occlusion[21] or after development of a traumatic coronary artery fistula[22] or traumatic coronary artery occlusion.[23] Such observations suggest that collaterals in our patients increased after and in response to reocclusion or persistent occlusion of the infarct-related artery, although we do not know how rapidly this occurred or if the abruptness of reocclusion had any effect on extent of collateralization.

Collaterals and left ventricular function: At initial angiography there was no difference between group 1 and 2 in the degree of collateralization or LVEF, nor did LVEF differ at follow-up angiography. This is not surprising, as the amount of viable, functioning myocardium, dependent upon the extent of myocardial necrosis as well as preexisting ventricular function, is likely to be determined early in AMI.

Despite a relative paucity of collaterals at initial angiography, there was a relation between the degree of collateralization and subsequent improvement in LV function. Of the 46 patients with total occlusion of the infarct-related artery in the early hours of AMI, patients who had an increase in LVEF in the interval between studies tended to have more intense and more extensive collaterals than did those whose LVEF subsequently failed to improve. However, there was a good deal of variance in collaterals (Fig. 6). The group of 15 patients in whom EF improved included the 4 patients (27%) with the highest collateral intensity or percent of distal infarct-related artery visualized, but it also included 4 patients with no collaterals at baseline. In contrast, of the 28 patients in whom EF did not improve, 16 (57%) had no angiographically visbile collaterals early in the course of infarction.

The protective effect of collaterals on LV function is a major source of controversy. Pertinent to this study is the effects of collaterals on LVEF during the dynamic state of evolving AMI. Our data support the hypothesis that the degree of collateralization to the infarct-related coronary artery has a potential beneficial effect on subsequent improvement in LVEF, but that this is a variable effect. Multivariate analysis of the patients in this study shows that collaterals are one of several independent factors associated with improvement in LV function.[24] Other factors may include shorter time to reperfusion[10] and lower baseline EF.[24] Our findings are in agreement with those of Rentrop et al,[7] who reported a modest increase in EF after AMI in a group of patients with collaterals to the infarcting area before receiving streptokinase, but no change in the EF in a group lacking collaterals before streptokinase treatment.[7] In addition, their findings suggested that the critical interval for myocardial salvage and improvement in EF was longer in patients with well-developed collaterals. In a small series of patients, Schwartz et al[10] found that early reperfusion had a beneficial effect on late EF in association with the presence of collaterals, as well as a shorter duration of ischemia and smaller area of ischemic risk.

Limitations of the study: The patients in this study all received some reperfusion intervention. The persistence or regression of collaterals is not necessarily what would occur in a patient with evolving AMI who is not treated with such interventions. Although the endpoint (vessel patency) is the same, streptokinase or percutaneous transluminal coronary angioplasty may affect collaterals in ways apart from their effects on vessel patency and degree of stenosis, and the conclusions drawn from this study may not be valid in the natural history of evolving AMI.

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Frequency and Significance of Induced Sustained Ventricular Tachycardia or Fibrillation Two Weeks After Acute Myocardial Infarction

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Electrophysiologic study, 24-hour ambulatory electrocardiographic monitoring, treadmill exercise test and angiographic evaluations were performed in 45 patients 14 ± 3 days (mean ± standard deviation) after acute myocardial infarction. Electrophysiologic study protocol included burst ventricular pacing and 1 to 3 ventricular extrastimuli at 2 cycle lengths from right ventricular apex, right ventricular outflow and left ventricle. Sustained monomorphic ventricular tachycardia (VT) (13 patients) or ventricular fibrillation (VF) (7 patients) was induced in 20 patients (44%) (group I). In these 20 patients, VT/VF was inducible with 2 extrastimuli in 10 patients, 3 extrastimuli in 9 patients and burst pacing in 1 patient. In the remaining 25 patients (56%), induction of no fewer than 7 ventricular beats were noted (group II). Severe left ventricular (LV) wall motion abnormalities occurred in 70% of group I patients and 22% of group II patients ($p < 0.005$). There was no difference in the site of infarction, frequency and grade of ventricular ectopic rhythm on ambulatory electrocardiographic monitoring, double product on submaximal exercise, LV ejection fraction, and number of obstructed coronary arteries (70% or greater) ($p > 0.1$) between group I and group II patients. During a mean follow-up of 10 ± 3 months, 1 patient in each group died suddenly, and in 1 group I patient spontaneous sustained VT developed which was identical in morphologic configuration to that induced during electrophysiologic study.

In conclusion, electrical induction of sustained VT or VF during electrophysiologic study is common in patients 2 weeks after acute myocardial infarction. These patients have an increased incidence of LV wall motion abnormalities. The prognostic significance of this finding requires further follow-up study but appears to be of limited value.

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Patients discharged from the hospital after an acute episode of myocardial infarction (MI) are at an increased risk of death particularly during the first year after this event.[1–6] The presence of left ventricular (LV) dysfunction, frequent and complex ventricular ectopic rhythms on ambulatory electrocardiographic monitoring, and myocardial ischemia or angina during low-level treadmill testing identifies a high-risk subgroup among these patients.[1–5,7–9] However, these variables lack sensitivity and specificity and may not warrant specific intervention in a given patient.[5]

Electrophysiologic studies have been shown to be useful in the management of patients with ventricular tachycardia (VT) and patients with out-of-hospital cardiac arrest due to ventricular fibrillation (VF).[10–13] Preliminary studies by Hamer et al[14] and Richards et al[15] in patients with acute MI suggested that programmed ventricular stimulation may be useful in identifying a subgroup of patients at high risk of sudden cardiac death. Therefore, we prospectively performed electrophysiologic, ambulatory electrocardiographic, exercise treadmill and angiographic studies in patients with acute MI in order to evaluate the relation between the response to programmed stimulation and the angiographic and other findings; and to determine the usefulness of programmed ventricular stimulation as a marker for the development of subsequent VT or sudden death.

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Methods

Patients: From September 1983 to July 1984, 102 patients were admitted to the coronary care unit of Los Angeles County–University of Southern California Medical Center with a confirmed diagnosis of acute MI. Eighty-four of them had transmural infarction and were considered for inclusion in the study. Criteria for transmural infarction were: ischemic chest pain lasting longer than 30 minutes, characteristic rise and fall of the serum CK level and its MB isoenzyme fraction, and characteristic evolutionary ST-T changes with the de-

velopment of new q waves over 2 or more frontal or precordial leads. There were 9 inhospital deaths. Thirty patients were excluded: 9 because of the presence of unstable angina or uncontrolled heart failure in the postinfarction period; 2 because they were older than 70 years; 7 because of end-stage disease of other organ system; and 12 because of refusal to have the studies performed. The remaining 45 patients agreed to have the studies performed and form the basis of this report. There were 41 men and 4 women, aged 35 to 67 years (mean standard deviation 52 ± 9). Twenty-two patients had anterior and 23 had inferior MI. Peak CK was 2,003 ± 1,552 units with an MB isoenzyme fraction of 16 ± 9% (normal, less than 5%). Thirteen patients had mild congestive heart failure (New York Heart Association class I or II) and 10 had mild angina after infarction. Except for 3 patients in whom primary VF developed during the first 24 hours of hospitalization, none had sustained VT or VF before the study.

The studies were performed 9 to 21 days after infarction and consisted of (1) 24-hour ambulatory electrocardiographic monitoring, (2) low-level treadmill exercise test, (3) programmed ventricular stimulation and (4) cardiac catheterization with coronary angiography. The last 2 studies were done on the same day. The longest interval between all 4 tests were never more than 7 days. Each patient gave informed consent. None of the 45 patients received antiarrhythmic agents or β-blocking drugs at the time of study. Nitrates (37 patients), digoxin (5 patients), diuretic drugs (13 patients) and calcium blockers (6 patients) were discontinued 24 hours before programmed ventricular stimulation. On the day of the study, the serum potassium level was normal (range 3.5 to 5.2 mEq/liter) in all patients, and the serum digoxin level ranged from 0.7 to 1.2 ng/ml in those taking digoxin.

Programmed ventricular stimulation: Programmed ventricular stimulation was performed with patients in the fasting and nonsedated state. A No. 6 quadripolar electrode catheter was introduced percutaneously into the right femoral vein and was first positioned at the right ventricular (RV) apex and then the RV outflow tract for stimulation. If necessary, a second No. 6 Fr electrocatheter was introduced percutaneously into the right femoral artery and advanced to the LV apex for LV stimulation. Surface electrocardiographic leads V_1, I and aVF, as well as RV and LV electrograms, were stimultaneously displayed and recorded on an oscilloscopic photographic recorder (Electronics for Medicine, VR-16) at speeds of 25 to 100 mm/s. Stimuli 2 ms in duration and twice the diastolic threshold were provided by a digital programmable stimulator (Bloom & Associates, Ltd). The stimulation protocol included burst ventricular pacing between cycle lengths of 400 to 250 ms, and single (S_1S_2), double ($S_1S_2S_3$) and triple ($S_1S_2S_3S_4$) extrastimuli at 2 driven cycle lengths of 500 and 400 ms. In all patients stimulation was begun at the RV apex with burst pacing and was followed by single and then double extrastimuli. If sustained VT or VF was not induced, the same stimulation sequence was applied to the RV outflow tract and then to the LV apex. When double extrastimuli failed to induce sustained VT or VF, a third ventricular extrastimuli was added and the same stimulation protocol was repeated at all 3 sites. The study was terminated when sustained VT or VF was induced, and was usually completed within 20 minutes.

Sustained VT was defined as VT that lasted longer than 30 seconds or that caused hemodynamic compromise requiring termination by overdrive pacing or cardioversion in less than 30 seconds.[10–13] *Nonsustained VT* was VT that lasted from 6 beats to 30 seconds and terminated spontaneously. *VF* was defined as organized or disorganized ventricular activity with a cycle length of less than 200 ms requiring immediate defibrillation.

Cardiac catheterization and coronary angiography: Right- and left-sided cardiac catheterization and LV and coronary angiography were performed after programmed ventricular stimulation. Pressures were recorded using Statham P23Db transducers and cardiac output was determined by the thermodilution technique. LV angiograms were performed in the 30° right anterior oblique (44 patients) and 55° left anterior oblique projections (43 patients), while coronary anteriograms were taken in multiple views using 35-mm cineangiography (44 patients). In 1 patient, LV catheterization and coronary angiography could not be performed because of technical difficulty in negotiating the catheter across the tortuous iliac artery system.

LV end-diastolic and end-systolic volumes and ejection fraction were calculated from the right anterior oblique projection using the area-length method.[16] Both LV and coronary angiograms were evaluated by 2 of us. If disagreement occurred, the film was reviewed by a third observer to obtain a consensus. The criterion for a "significant" stenosis was 70% or more reduction in internal diameter of these vessels. For the left main coronary artery, a 50% or greater reduction in internal diameter was considered significant. The circumflex artery was considered involved if its main vessel or the large obtuse marginal branch was stenotic. Stenoses involving only the branches of left anterior descending or right coronary arteries was not counted. Left main stenosis was classified as 2-vessel disease. No major vessel was counted twice.

The LV angiograms were analyzed for wall motion in *both* right anterior oblique and left anterior oblique projections (43 patients) using the method previously described.[17] Each projection was divided into 5 equal segments and a quantitative wall motion score was determined from the analysis of 10 segments. The contraction of each segment was scored as follows: normal = 1, moderate hypokinesia = 2, severe hypokinesia = 3, akinesia = 4, and dyskinesia = 5.[17] The total score was obtained by adding the values assigned to each segment. With this system, a score of 10 equals normal wall motion function, 10 to 15 indicates a mild motion abnormality, 15 to 25 a moderate wall motion abnormality, and more than 25 severe wall motion abnormality.

Ambulatory electrocardiographic monitoring: All patients underwent 24-hour continuous ambulatory electrocardiographic monitoring 6 to 17 (mean 10 ± 3) days after infarction. Two-channel high-fidelity cassette recordings were analyzed for frequency, morphologic characteristics and timing of premature ventricular complexes using a Del Mar Avionics system.

Treadmill exercise test: Thirty-five patients underwent a low-level treadmill exercise test according to a modified Sheffield's protocol 7 to 14 days (mean 10 ± 2) after infarction. The exercise was continued until a target heart rate of 120 beats/min was achieved or the patient had angina, 0.2 mV horizontal or downsloping ST-segment depression, marked fatigue, high-grade ventricular ectopy or systolic hypotension of 20 mm Hg or more. A result was considered positive when any recorded lead during exercise or during recovery showed a horizontal or downsloping ST-segment depression of 0.1 mV or more at 80 ms after the J point.

Follow-up study: Patients were followed in the cardiology clinics of the Los Angeles County-University of Southern California Medical Center at intervals of 4 to 8 weeks; some were followed by their private physicians. If a patient died, the circumstance of the event was determined. Sudden death was defined as death that occurred within 1 hour after the onset of terminal symptoms or when death occurred unexpectedly without premonitory symptoms.

Statistical analysis: Values are expressed as mean ± standard deviation. Patients with and without induction of

TABLE I Clinical Characteristics

Variable	Group I (n = 20)	Group II (n = 25)	p Value
Age (yr)	51 ± 8*	53 ± 9*	NS
Men (n)	18 (90)	23 (92)	NS
History of			
MI	1 (5)	3 (12)	NS
Hypertension	12 (60)	8 (32)	0.08
Diabetes mellitus	5 (25)	5 (20)	NS
Peak CK (U)	2,551 ± 1,734*	1,579 ± 1,280*	0.09
Anterior MI (%)	12 (60)	10 (40)	NS
After MI			
Heart failure†	9 (45)	4 (16)	<0.05
Angina pectoris†	6 (30)	4 (16)	NS
Interval between acute MI and PVS (days)	15 ± 3*	13 ± 3*	<0.05
Duration of exercise (min)	7.7 ± 2*	8 ± 2*	NS
Exercise-induced ST depression (%)	29	33	NS

* Standard deviation.
† Mild and easily controlled with "medical" therapy.
Numbers in parentheses are the percentages.
MI = myocardial infarction; NS = not significant; PVS = programmed ventricular stimulation.

sustained VT or VF were compared using a chi-square test or Student *t* test. The difference was considered statistically significant when the p values were ≤0.05 and not statistically significant when the p value was >0.1. The p values between 0.05 and 0.1 are given.

Results

Induction of ventricular tachycardia or ventricular fibrillation: Programmed ventricular stimulation induced sustained monomorphic VT in 13 patients and polymorphic VT that degenerated into VF in 7 patients. Thus, 20 of the 45 patients (44%) (group I) had induction of sustained VT or VF. In 13 patients with induction of sustained monomorphic VT, the QRS morphologic pattern was of right bundle branch block pattern in 9 and a left bundle branch pattern in 4; the cycle length ranged from 200 to 270 ms (mean 228 ± 23). VT could be terminated by overdrive pacing in 6 patients and required cardioversion in 7. All 7 patients with induction of polymorphic VT that degenerated into VF required immediate direct-current cardiac shock. Sustained VT or VF was induced from the right ventricle in 15 patients and the left ventricle in 5. It was induced by burst pacing in 1 patient, double ventricular extrastimuli in 10 patients and triple ventricular extrastimuli in 9 patients.

Of the remaining 25 patients (group II), 1 had induction of nonsustained monomorphic VT lasting for a maximum of 7 beats; the induction required double extrastimuli at the RV apex. Five patients had induction of repetitive ventricular responses of maximum 3 to 5 beats with triple extrastimuli, and 19 patients had induction of no ventricular responses during the study.

Comparison of patients with and without induction of sustained ventricular tachycardia or ventricular fibrillation: Group I patients had higher levels of serum CK and increased incidence of heart failure (Table I). The mean interval between infarction and programmed ventricular stimulation was longer in group I than in group II (15 ± 3 vs 13 ± 3 days, p <0.05). There were no significant differences between the 2 groups in the mean frequency or incidence of repetitive forms of ventricular premature complexes detected during 24-hour ambulatory monitoring (Fig. 1). Two groups did not differ significantly with regard to the findings on treadmill testing (Table I), angiographic LV ejection fraction (0.45 ± 0.1 vs 0.50 ± 0.1, p >0.1), LV end-diastolic pressure (24 ± 8 vs 24 ± 9 mm Hg) and LV stroke work index (41 ± 17 vs 48 ± 14 g-m/m^2).

Mean LV wall motion score was significantly higher in group I than in group II, 22 ± 6 vs 17 ± 5 (p <0.005) (Table II). Fourteen of the 20 patients (70%) with inducible sustained VT or VF (group I) had moderate to severe wall motion abnormalities with a wall motion score of at least 20, compared with 5 of the 23 patients (22%) without inducible VT or VF (group II) (p <0.005). Group I patients also had a significantly higher inci-

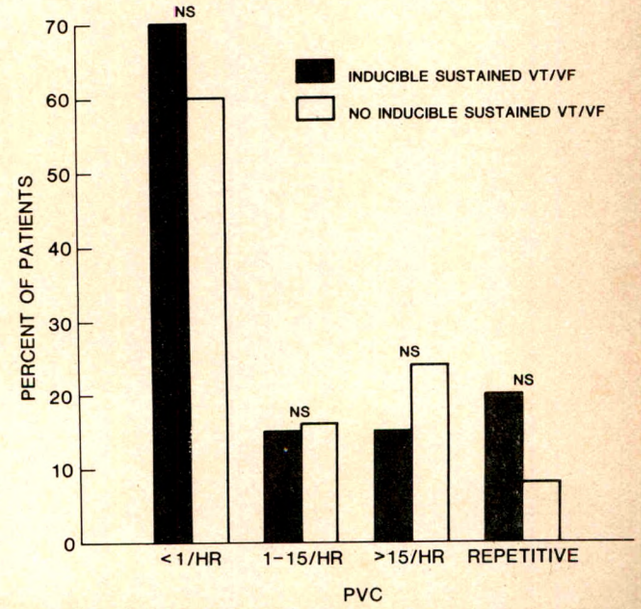

FIGURE 1. Twenty-four-hour ambulatory electrocardiographic monitoring data in patients with and without inducible sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). NS = not significant; PVC = premature ventricular contractions.

TABLE II Left Ventricular Angiographic Wall Motion Abnormalities

	Group I (n = 20)	Group II (n = 23)	p Value
Wall motion score			
10–15	2 (10)	8 (35)	0.07
16–20	4 (20)	10 (43)	NS
21–25	10 (50)	4 (17)	<0.05
>25	4 (20)	1 (5)	NS
Type of wall motion abnormality			
None	0 (0)	1 (4)	NS
Hypokinesia only	3 (15)	8 (35)	NS
Akinesia	12 (60)	10 (43)	NS
Dyskinesia	10 (50)	6 (26)	NS
Aneurysm	9 (45)	3 (13)	<0.05

Numbers in parentheses are percentages.
NS = not significant.

dence of LV aneurysms than group II patients (45 vs 13%, p <0.05) (Fig. 2). Coronary angiography showed that 14 patients (32%) had 1-vessel disease, 14 (32%) had 2-vessel and 15 (34%) had 3-vessel disease. In 1 patient, the coronary arteries were normal. Twenty-three of the 44 patients (52%) had complete occlusion of at least 1 major vessel. There was no significant difference in the number or distribution of diseased vessels between the 2 groups. Main left coronary artery stenosis was observed in only 1 patient, who was in group II.

Treatment and follow-up observations: Of the 13 group I patients with inducible sustained monomorphic VT, 10 underwent electropharmacologic testing with intravenously administered procainamide (loading dose: 15 mg/kg body weight followed by a constant infusion at 2 mg/min). Although procainamide prevented induction of VT (more than 6 beats) in only 3 patients, all 10 were discharged with oral procainamide 3 to 4 g/day. This therapy, however, was discontinued 2 to 3 months after discharge in all except 2 patients, who have been maintained with procainamide treatment at the discretion of their attending physicians. All other patients were discharged from the hospital without any specific antiarrhythmic therapy. None of the 45 patients received a β-blocking agent. Two patients in each group underwent coronary bypass surgery for either left main coronary disease (1 patient) or persistent angina refractory to medical therapy (3 patients).

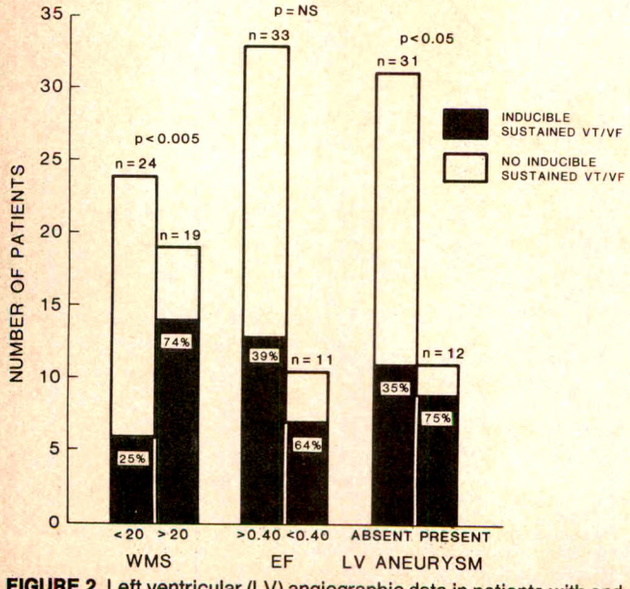

FIGURE 2. Left ventricular (LV) angiographic data in patients with and without inducible sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). EF = ejection fraction; NS = not significant; WM = wall motion score.

The follow-up of these 45 patients ranged from 4 to 17 months (mean 10 ± 3). Thirty-six were followed in the Cardiology Clinic of Los Angeles County–University of Southern California Medical Center, and in 7 patients the follow-up data were obtained by telephone from their referring physicians (2 patients), the patients themselves (3 patients) or their family (2 patients). Two patients in group II were lost to follow-up 4 and 5 months, respectively, after discharge from the hospital. During the follow-up period 2 patients died suddenly; 1 had inducible sustained VT (group I) and the other had induction of no more than 5 repetitive beats (group II). Sudden death occurred 17 and 2 months, respectively, after the index MI, and at the time of its occurrence both patients were taking no antiarrhythmic agents. One group I patient had spontaneous sustained VT (nonfatal) 25 days after the index MI. This VT was identical in morphologic pattern to the one induced during programmed ventricular stimulation. There have been 2 nonsudden deaths; 1 group I patient died from intractable cardiac failure 10 months after the index infarction and 1 group II patient who was asymptomatic and taking no specific therapy had a suicidal death 72 days after the initial infarction. The remaining 38 patients were still alive and have had no documented occurrence of sustained VT/VF during a follow-up of 8 to 17 months (mean 12 ± 4). Two patients (group I) have had recurrent episodes of heart failure and 1 patient (group I) sustained an uncomplicated subendocardial infarction 3 months after the index infarction.

Discussion

The survivors of acute MI after discharge from the hospital are at increased risk of death during the first year after their event, with an average mortality rate of 7 to 11%.[1–6] Sudden cardiac death accounts for half of these deaths and is usually a result of VT or VF. Programmed ventricular stimulation has been shown to be useful in the diagnosis and management of patients with recurrent sustained VT or out-of-hospital cardiac arrest.[10–13] Therefore, one may hypothesize that programmed ventricular stimulation would be helpful in predicting patients at high risk of sudden death in the first year after MI, and preliminary data by Hamer et al[14] and Richards et al[15] appear to confirm this. Hamer et al studied 70 patients with recent MI complicated by heart failure or arrhythmias or both. They found that induction of 5 or more repetitive ventricular responses identified a high-risk subgroup of 12 patients, of whom 4 died suddenly during a 12-month follow-up period. However, 5 of their remaining 58 patients without induction of 5 or more repetitive ventricular responses also died suddenly during follow-up. Thus, they had studied selected patients and their findings had low specificity. Richards et al studied 165 hemodynamically stable patients 6 to 28 days (mean 10) after MI. Of the

38 patients with induction of VT lasting longer than 10 seconds, 8 died suddenly during a mean follow-up period of 8 months, whereas none of the remaining 127 patients without induction of VT encountered sudden death. In contrast, Marchlinski et al[18] studied 46 patients with recent infarction and found that only 1 of the 10 patients with induction of sustained or nonsustained VT died suddenly during a mean follow-up period of 18 months, whereas 5 of the remaining 36 patients without induction of VT died suddenly.[18] These conflicting results may be a result of significant differences in patient selection, protocols for stimulation during the electrophysiologic study and definition of positive responses. Moreover, none of these studies correlated the induction of VT or VF with the severity of coronary artery disease, hemodynamic or angiographic parameters.

In the present study, we excluded patients with uncontrolled heart failure or unstable angina because such patients are at high risk, and the patients with unstable angina have an excellent response to coronary bypass surgery.[19–21] A vigorous stimulation protocol was used that consisted of triple ventricular extrastimuli from both the right and left ventricles. Programmed stimulation using this protocol has been reported to induce clinical arrhythmias in 80 to 98% of the patients who present with recurrent sustained VT or cardiac arrest.[10,11,22] Also, in patients without documented ventricular arrhythmias, sustained VT is almost never induced and the induction of VF is infrequent.[22–24] Two weeks after MI, we could induce sustained VT or VF in 22% of patients with double extrastimuli and in 44% with triple extrastimuli. The patients in whom sustained VT or VF was induced had more severe wall motion abnormalities, had an increased incidence of mild heart failure and LV aneurysms and tended to have lower LV ejection fractions and larger infarcts judged by peak CK values. These findings are in accord with previous observations made in the survivors of out-of-hospital cardiac arrest in whom the presence of moderate to severe LV wall motion abnormalities was associated with more frequent induction of VT or VF,[25] as well as an increased incidence of recurrent cardiac arrest.[26] Our findings are also in accord with canine ischemic models in which electrical instability occurred more often with a large infarct.[27]

The relatively short term follow-up and the small number of patients in our study do not permit us to determine whether programmed ventricular stimulation identifies patients after infarction who are at high risk of sudden death. However, the inducibility of sustained VT/VF 14 ± 3 days after acute MI did not appear to have clinical significance during the mean follow-up of 10 ± 3 months. Whereas 44% of the patients had inducible sustained VT or VF, only 1 had spontaneous sustained VT and 1 died suddenly during the follow-up period. The other sudden death occurred in a patient who had no inducible VT. The study raises an important question as to the clinical significance of inducible sustained VT or VF during the early period after infarction. In a study of 40 patients with sustained VT that occurred within 2 months after infarction, Marchlinski et al[28] induced nonclinical forms of sustained VT in 45% of patients. Kowey et al[29] induced sustained VT in 5 of 57 asymptomatic patients (9%) with recent infarction; 4 were studied within 3 months of infarction. Buxton et al[30] studied a group of 33 patients with stable coronary artery disease and nonsustained VT; 13 (40%) had induction of sustained VT or VF. Recent MI may provide an anatomic substance for induction of VT or VF that has little long-term clinical significance. These questions must be answered by additional studies, because the inducibility of sustained VT or VF may decline 3 to 6 months after infarction; however, the high incidence of sudden death also declines 6 months after MI.

Ten of the 20 patients with inducible sustained VT/VF (group I) received antiarrhythmic therapy. This therapy may have influenced the subsequent posthospital course of these patients. However, this is less likely because acutely administered procainamide in the laboratory failed to suppress induction of VT in most of these patients, and antiarrhythmic therapy was discontinued 2 to 3 months after the index infarction in almost all of them. Moreover, there are no data that indicate a beneficial effect of antiarrhythmic therapy on the survival of patients after MI.

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Crossover from Intravenous to Transdermal Nitroglycerin Therapy in Unstable Angina Pectoris

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The present study was designed to examine the safety and efficacy of titrating a nitroglycerin infusion to a fixed hemodynamic endpoint as initial therapy for patients admitted to a coronary care unit for medically refractory unstable angina, and to test the hypothesis that patients, responding to the addition of intravenous (i.v.) nitroglycerin to their previous antianginal regimen, could be crossed over to nitroglycerin administered by a new transdermal delivery system. In 9 patients the nitroglycerin infusion titrated upward at 3- to 10-minute intervals until a 10% reduction in mean arterial pressure was achieved. This titration schedule and hemodynamic endpoint proved safe and effective for controlling episodes of chest pain at rest in all 9 patients. Subsequently, this treatment strategy was tested in 17 consecutive patients with unstable angina treated in our coronary care unit during a 1-month period. In 10 of 15 successfully treated patients ischemia was the cause of chest pain as documented by cardiac catheterization. No change was made in antianginal or vasoactive drugs during the period of i.v. nitroglycerin administration or during crossover to transdermal therapy. In this well defined subgroup of patients with unstable angina, nitroglycerin infusion decreased the mean arterial pressure from 101 ± 18 to 87 ± 11 mm Hg (mean ± standard deviation), using an infusion rate of 84 ± 74 μg/min (range 10 to 200). The mean duration of i.v. therapy was 36 ± 12 hours. In 4.8 ± 0.9 hours, all 10 patients were weaned off i.v. therapy and crossed over in a stepwise fashion to a mean dose of 22.5 ± 10 mg/24 hours of transdermal nitroglycerin patches (range 5 to 40 mg/24 hours), while maintaining the mean arterial pressure reduction previously achieved after initiation of i.v. therapy. Mean arterial pressure was 86 ± 11 mm Hg with i.v. therapy immediately before crossover and was maintained at 83 ± 9 and 85 ± 11 mm Hg 1 and 24 hours after crossover to transdermal nitroglycerin therapy, respectively. Two patients had episodes of chest pain during the first 24 hours of transdermal therapy. Both became pain free after upward titration of the transdermal dose by 10 mg/24 hours. Among these 10 patients, 7 had no further episodes of pain throughout the remainder of their hospitalization. One patient had a single episode of chest pain after transient interruption of transdermal nitroglycerin therapy and 1 patient had a single episode of pain after transient reduction in the transdermal dose. These results suggest that i.v. nitroglycerin, titrated to reduce mean arterial pressure by 10% is safe and effective treatment for patients with unstable angina admitted to a coronary care unit, and that the new transdermal nitroglycerin delivery systems can be used successfully to maintain the beneficial antiischemic effects initially achieved with i.v. nitroglycerin therapy.

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Sublingual nitroglycerin has been successfully used to treat episodes of angina pectoris for more than 100 years.[1] Although the use of intravenous (i.v.) nitroglycerin was first reported more than 20 years ago,[2] it was only released for clinical use by the Food and Drug Administration in October 1981. Subsequently, several

TABLE I Patient Groups

Pt.	Sex & Age (yr)	Diagnosis	Prior Infarction	Anginal Duration (mo)	Cath. Findings
		Prospective Intravenous Nitroglycerin Titration Study			
1	F52	UA-p̄-MI	+	84	3V
2	M71	UA	0	18	3V
3	M53	UA	+	120	3V
4	M71	UA	+	120	3V
5	F65	UA	+	12	2V
6	M76	UA	0	60	3V
7	F64	UA	0	0	—
8	M53	UA	0	120	2V & LM
9	M66	UA	0	24	1V
		Retrospective Intravenous to Transdermal Nitroglycerin Crossover Study			
1	M75	UA	0	6	3V
2	M50	UA	+	36	3V
3	M55	UA	+	72	3V & LM
4	M81	UA-p̄-MI	+	0	—
5	M65	UA	+	9	3V
6	F70	UA	0	36	2V & LM
7	F62	UA-p̄-MI	+	1	3V
8	M62	UA-p̄-MI	+	84	3V
9	M53	UA	0	120	2V
10	M55	UA-p̄-MI	+	72	3V
11	F63	UA	0	12	—
12	F75	UA	+	48	—
13	M38	UA-p̄-MI	+	27	Spasm
14	F63	UA	0	12	No CAD
15	F65	UA	0	13	No CAD
16	M75	UA-p̄-MI	+	120	3V
17	M70	UA	+	240	3V

CAD = coronary artery disease; Cath. = catheterization; LM = left main coronary artery disease; p̄-MI = after acute myocardial infarction; UA = unstable angina; 1V, 2V and 3V = 1, 2 and 3-vessel disease, respectively; + = yes; 0 = no; — = none.

studies have demonstrated beneficial effects of adding i.v. nitroglycerin to prior medical therapy in patients admitted to a coronary care unit with the diagnosis of unstable angina.[3–5] If episodes of chest pain at rest are brought under control with i.v. nitroglycerin therapy, and if one wishes to continue nitrate therapy, it would be necessary to switch to a route of administration that could be continued on a regular medical floor and then on an outpatient basis. Sublingual, buccal, oral and topical nitrate preparations with durations of action of 1½ to 6 hours are available. However, all require multidose administration for continuous prophylactic therapy. Recently, transdermal delivery systems have been developed that propose to deliver nitroglycerin continuously for 24 hours.[6]

The present study has 2 parts. The first part is a prospective study that tested the hypothesis that a 10% reduction in mean arterial pressure is a safe and effective initial endpoint for the titration of i.v. nitroglycerin in patients with unstable angina. The second part is a retrospective study that tested the therapeutic strategy of adding i.v. nitroglycerin to prior medical therapy and also tested the hypothesis that patients whose unstable angina is controlled after the addition of i.v. nitroglycerin could be crossed over to transdermal nitroglycerin with continued control of their episodes of chest pain at rest.

Methods

Patient groups: *Prospective study:* Nine nonconsecutive patients admitted to The Johns Hopkins Hospital Coronary Care Unit with the diagnosis of unstable angina were entered into the prospective study, which tested the safety and efficacy of a 10% reduction in mean arterial pressure as the initial titration endpoint for i.v. nitroglycerin therapy (Table I). The study group consisted of patients who had had 1 or more episodes of chest pain at rest associated with at least 1 mm of ST-segment elevation or depression during the 12 hours before initiation of the nitroglycerin infusion. Patients were selected by daytime presentation and availability of the research nurse. Exclusion criteria included: (1) systolic blood pressure less than 100 mm Hg, (2) severe liver or renal disease, (3) suspected increased intracranial or intraocular pressure, and (4) constrictive pericarditis or pericardial tamponade.

All 9 patients had obtained relief of their last chest pain episode with 1 or more 0.4-mg sublingual nitroglycerin tablets. Seven of 9 patients were taking long-acting nitrates, 3 were taking β blockers and 4 were taking calcium channel blockers before admission to the coronary care unit (Table II). Cardiac catheterization was performed in 8 of 9 patients (Table I).

Retrospective study: Seventeen consecutive patients were admitted to The Johns Hopkins Hospital Coronary Care Unit during a 1-month period with unstable angina or acute myocardial infarction (AMI) with the subsequent development of angina at rest. All were under the care of 1 cardiologist (J.T.F.) and all, therefore, were treated with a single therapeutic strategy. Two patients (nos. 16 and 17) still had chest pain after the addition of i.v. nitroglycerin and therefore underwent urgent coronary bypass surgery (Table I). Ten of the remaining 15 patients, having responded to the addition of i.v. nitroglycerin, had their infusion tapered and crossover to transdermal therapy accomplished *without* alteration of their concurrent medications and without addition of other antianginal or vasoactive (e.g., antihypertensive) medications. In these 10 patients an ischemic etiology for chest pain was documented by coronary angiography (9 patients) or by a documented MI (1 patient) (Table I). The remaining 5 patients

TABLE II Prior Medications and Clinical Outcomes

Pt.	Long-Acting Nitrates (dose/24 hours)	β Blockers (mg/24 hours)	Ca^{++} Blockers (mg/24 hours)	Chest Pain During Titration	Final i.v. Infusion Rate (μg/min)	Chest Pain After i.v. Endpoint Reached
			Prospective Intravenous (i.v.) Nitroglycerin Titration Study			
1	Paste 18″	P80	0	0	5	0
2	0	0	N80	0	56	0
3	0	0	V120	+	15	0
4	Paste 20″	0	0	0	88	0
5	Paste 7.5″	0	0	0	250	0
6	TD 10 mg/24 hours	P60	0	0	18	0
7	TD 15 mg/24 hours	P40	N40	+	16	0
8	ISDN 120 mg	0	N40	0	8	0
9	Paste 9″	0	0	0	12	0

Pt.	Long-Acting Nitrates (dose/24 hours)	β Blockers (mg/24 hours)	Ca^{++} Blockers (mg/24 hours)	Final i.v. Infusion Rate (μg/min)	Chest Pain After i.v. Endpoint Reached	Final TD-NTG Dose (cm^2)	Chest Pain on Initial TD Dose
			Retrospective Intravenous to Transdermal Nitroglycerin Crossover Study				
1	Paste 12″	A50	N120	60	0	50	0
2	0	P80	N120	60	0	30	0
3	ISDN 60 mg	P160	N40	10	0	10	0
4	0	0	0	50	0	40	0
5	ISDN 60 mg	0	V640	16	0	(20) 40	+
6	0	0	0	200	0	70	0
7	TD 5 mg/24 hours	0	N80	(110) 160	1	50	0
8	Paste 24″	0	V240	196	0	40	0
9	ISDN 80 mg	0	N80	14	0	40	0
10	ISDN 160 mg	0	N160	44	0	(60) 80	+

Values in parentheses indicate dose after titration to the hemodynamic endpoint, before upward titration to the final dose after a chest pain episode.

A = atenolol; ISDN = isosorbide dinitrate; N = nifedipine; NTG = nitroglycerin; P = propranolol; Paste = 2% nitroglycerin ointment; TD = transdermal nitroglycerin patch; V = verapamil; 0 = absent; + = present.

either required addition of other vasoactive drugs or did not have an ischemic cause for their chest pain documented. Two patients (nos. 11 and 12) with a prior history of hypertension required the addition of oral hydralazine or alpha methyldopa during crossover in order to control blood pressure. One patient (no. 13) had coronary spasm with near-normal coronary arteries demonstrated on coronary angiography and therefore had his dose of calcium blocker (nifedipine) increased empirically. The final 2 patients (nos. 14 and 15) had normal coronary arteries demonstrated on coronary angiography with negative results on ergonovine stimulation tests.

The transdermal nitroglycerin delivery systems maintained control of chest pain at rest in all 15 patients initially responding to the addition of i.v. nitroglycerin to their prior medical therapy. However, this study concentrates attention on the 10 patients with a documented ischemic cause for their chest pain and no change in antianginal or other vasoactive drugs during crossover (patients 1 to 10, Table I). In this well-defined subgroup, there were 8 men and 2 women (7 white and 3 black) and the mean age was 63 ± 10 years (± standard deviation). Six patients had an admission diagnosis of unstable angina. Four patients had AMI documented by an increase in MB–creatine kinase blood levels, and subsequently had unstable angina without reelevation of cardiac enzymes. Seven of the 10 patients had a history of MI. The mean duration of stable exertional angina before the present admission was 41 ± 42 hours. Four patients had undergone coronary artery bypass surgery and 1 patient had undergone transluminal angioplasty. All 6 patients with unstable angina without recent AMI had had multiple episodes of chest pain at rest during the 24 hours before admission to the coronary care unit. The 4 patients with post MI unstable angina had at least 1 episode of chest pain at rest during the 3 hours before the initiation of i.v. nitroglycerin therapy. All had obtained relief of their last chest pain episode with 1 or more sublingual nitroglycerin tablets (mean dose 1.1 ± 0.6 mg). Eight of the 10 patients were receiving calcium channel blockers and 3 patients were receiving β blockers before admission (Table II). In all patients, calcium channel blocker and β-blocker therapy was continued at the same doses given when they entered the coronary care unit during i.v. nitroglycerin therapy, during the subsequent crossover period and for at least 24 hours thereafter.

Experimental protocol: *Prospective study:* Baseline mean arterial pressure was determined by averaging 6 measurements of blood pressure taken at 5-minute intervals over a 30-minute period. Blood pressure was measured using an ultrasonic blood pressure cuff (Infrasonde), which displays systolic, diastolic and mean arterial pressure. The nitroglycerin solution was prepared by adding a 10-ml ampule of Tridil® (American Critical Care) that contained 50 mg of nitroglycerin to 500 ml of 5% dextrose in water or 0.9% normal saline solution in glass bottles to produce a final concentration of 100 μg/ml. If the infusion rate exceeded 160 μg/min, then the concentration of nitroglycerin was increased to 400 μg/ml by adding 4 ampules to 500 ml. A special polyethylene plastic administration set (Tridil Set, American Critical Care), into which absorption of nitroglycerin is less than 1%, was used with all infusions. The i.v. infusion of nitroglycerin was administered with an IMED 922 infusion pump at an initial rate of 4 to 5 μg/min and the infusion rate increased at prescribed intervals until a 10% reduction in mean arterial pressure was reached or systolic pressure decreased to 90 mm Hg. Blood pressure was measured 3 minutes after each change in infusion rate. If mean arterial pressure decreased 3% or less from baseline, the infusion rate was immediately increased to the next level. Dose increments were set at 5 μg/min between 5 and 20 μg/min, 10 μg/min between 20 and 40 μg/min, 20

μg/min between 40 and 80 μg/min, 30 μg/min between 80 and 200 μg/min and then 40 μg/min between 200 and 640 μg/min. If the mean arterial pressure decreased 4 to 6% from baseline after 3 minutes, then no change in infusion rate was made for a total of 10 minutes. If after 3 minutes the initial decrease in mean arterial pressure was 7% or more, then the infusion rate was returned to the previous rate for 10 minutes and a one-half increment attempted. When mean arterial pressure approached the desired level, fine adjustments to achieve the exact hemodynamic endpoint were carried out with increments of less than 50% of the previous increment, at 10-minute or more intervals. Back titration was allowed if the reduction in mean arterial pressure exceeded 10% or if adverse reactions occurred. Episodes of chest pain with associated electrocardiographic changes occurring during the titration period were treated with sublingual nitroglycerin before continuing titration. Crossover to transdermal nitroglycerin before discharge from the coronary care unit was carried out without a specific crossover protocol by the patient's attending cardiologist.

Retrospective study: The infusion of nitroglycerin was initiated at 4 to 5 μg/min, and the infusion rate was increased stepwise until a 10 to 15% reduction in mean arterial pressure was achieved. The final i.v. infusion rate, once achieved, was maintained for 8 to 48 hours. If the patient remained pain free, crossover to transdermal nitroglycerin patches was begun. Crossover was initiated by reducing the infusion rate of i.v. nitroglycerin by approximately 50% and a 5-mg/24-hour transdermal nitroglycerin patch was applied (Nitrodur®, Key Pharmaceuticals). If after at least 30 minutes of observation the systolic blood pressure had not increased at least 10%, the i.v. infusion rate was decreased further. If the systolic blood pressure increased at least 10%, or an episode of chest pain occurred, then another 5- or 10-mg/24-hour nitroglycerin patch was added. This sequence was repeated until the i.v. infusion was discontinued with the patient's blood pressure remaining at or near the level achieved with i.v. nitroglycerin. In 3 patients (nos. 4, 5 and 6) with initially low arterial pressures (mean arterial pressure between 72 and 88 mm Hg) after an initial 3 to 10% reduction had been obtained by cautious titration, mean arterial pressure was observed to increase above control levels before crossover to transdermal therapy. In these 3 patients, transdermal patches were titrated to reduce mean arterial pressure approximately 10% below this new baseline level. Additional 5- or 10-mg/24-hour patches could be applied if an episode of chest pain occurred after the initial blood pressure endpoint had been reached.

Results

Prospective study: The mean final infusion rate of i.v. nitroglycerin required to obtain a 10% reduction in mean arterial pressure was 64 ± 80 μg/min (range 5 to 250). Although the formal experimental protocol was complete 1 hour after reaching the final maintenance infusion rate, clinical outcomes were recorded up to the time of the patient's discharge from the coronary care unit. After reaching the final infusion rate, no further episodes of chest pain at rest occurred in 8 of the 9 patients studied (Table I). The remaining patient had a single episode of chest pain after 24 hours of i.v. therapy, but had no additional chest pain episodes after a single additional upward titration. Two of these 9 patients (nos. 4 and 8) subsequently underwent bypass surgery, not because of a recurrence of unstable angina, but because of the severity of the fixed coronary disease documented at coronary angiography. One of these 2 patients (no. 4) was maintained with i.v. nitroglycerin until surgery. One patient (no. 1), after undergoing cardiac catheterization, was believed not to be a surgical candidate because of the presence of extremely severe distal vessel disease and poor left ventricular function. The patient remained pain free for 10 days with i.v. nitroglycerin therapy before dying from left ventricular failure. Seven patients, including 1 of the patients who underwent elective surgery, were weaned off i.v. nitroglycerin and switched to transdermal nitroglycerin patches (5 to 20 mg/24 hours) without a specific crossover protocol. No further chest pain episodes occurred after crossover in any of these 7 patients up to the time of their discharge from the coronary care unit.

Hemodynamic changes: Systolic pressure was reduced after the addition of i.v. nitroglycerin from 130 ± 15 to 116 ± 15 mm Hg, a 10.9 ± 6.2% reduction from control. Mean arterial pressure was similarly reduced from 95 ± 10 to 85 ± 9 mm Hg, a 10.6 ± 1.8% reduction from baseline (range 7 to 13%).

Clinical outcome: Three patients had transient episodes of chest pain during upward titration of the nitroglycerin infusion. Six patients had no alteration of their antianginal regimen with the exception of nitrates (Table II). In 1 patient nifedipine was increased from 40 to 80 mg/day and in another patient nifedipine was added at 120 mg/day for empirical reasons, despite no further episodes of chest pain after reaching the final infusion rate of i.v. nitroglycerin. In the remaining patient propranolol was increased from 60 to 80 mg/day, again despite no further chest pain having occurred.

Retrospective study: In the subgroup of 10 patients included in our retrospective study, the mean duration of i.v. nitroglycerin treatment was 36 ± 26 hours, and the mean final infusion rate was 84 ± 74 μg/min (range 10 to 200). One patient had a single episode of chest pain after the initial hemodynamic endpoint had been reached, prompting an additional upward step of titration to the final maintenance infusion rate. After the final maintenance infusion rate had been established, none of the 10 study patients had further episodes of chest pain. During the crossover period the i.v. infusion rate was decreased stepwise at 51 ± 31-minute intervals until the infusion was discontinued. Crossover was accomplished by stepwise addition of nitroglycerin patches at 104 ± 74-minute intervals using 5- or 10-mg/24-hour dose increments (mean 7.5 mg/24 hours), attempting to maintain as closely as possible the mean arterial pressure level achieved after initiation of i.v. therapy. Two patients (nos. 5 and 10) had an episode of chest pain during the first 24 hours after the initial blood pressure–defined crossover had been carried out. In both patients, an additional 10-mg/24-hour dose of transdermal nitroglycerin was required to restore blood pressure, which had increased during the interim from its initial level after crossover. Both patients remained pain free after this final transdermal dose was established (22.5 ± 10 mg/24 hours [range 5 to 40]). The mean interval required for crossover was 4.8 ± 2.8 hours.

Hemodynamic changes: Mean control systolic blood pressure was 138 ± 20 mm Hg. After institution of i.v. nitroglycerin therapy, systolic pressure was reduced to 117 ± 14 mm Hg, a mean decrease of 14 ± 8% from the

control level ($p < 0.001$) (Fig. 1). One hour after crossover to the transdermal nitrate preparation, systolic pressure was 114 ± 1 mm Hg, which was not significantly different from 112 ± 19 mm Hg measured just before the tapering of i.v. therapy was begun. Likewise, 24 hours after crossover, systolic pressure was 115 ± 15 (not significant [NS] vs levels after final i.v. or 1 hour after crossover). The mean control diastolic pressure was 82 ± 19 mm Hg, decreasing from 12 ± 5% to 73 ± 11 mm Hg after initiation of i.v. nitroglycerin ($p < 0.001$). One hour after crossover to transdermal therapy, diastolic pressure was 70 ± 8 mm Hg (NS vs 73 ± 10 mm Hg measured before tapering the i.v. infusion). The average control mean arterial pressure was 101 ± 18 mm Hg, decreasing from 12 ± 8% to 87 ± 11 mm Hg after titration of the i.v. infusion ($p < 0.001$) (Fig. 1). One hour after crossover to nitroglycerin by transdermal delivery, the mean arterial pressure was 85 ± 9 mm Hg (NS vs 86 ± 11 mm Hg measured just before crossover was begun). Likewise, 24 hours after crossover, mean arterial pressure was 85 ± 11 mm Hg (NS vs levels after final i.v. or 1 hour after crossover). The mean heart rate was 75 ± 18 beats/min during the control period, 75 ± 13 beats/min before tapering of i.v. nitroglycerin was begun, and 76 ± 11 beats/min 1 hour after crossover to transdermal therapy (NS).

Clinical outcome: During the 24-hour period after crossover to the final transdermal nitroglycerin dose, no further episodes of chest pain occurred in the 10 patients under discussion. Seven of the 10 patients had no further episodes of chest pain at rest during the remainder of their hospitalization and were discharged with the same medical regimen given at the time of their transfer from the coronary care unit. One patient (no. 1) had recurrent chest pain episodes at rest 8 days after discharge from the coronary care unit. This patient failed to respond to the reinstitution of i.v. nitroglycerin and immediately underwent coronary bypass surgery. The 2 remaining patients each had a recurrent episode of chest pain at rest after transdermal nitroglycerin therapy was discontinued (patient 4) or the dose was reduced (patient 8) 4 days after discharge from the coronary care unit. After transdermal nitroglycerin had been restarted (patient 4) or the dose restored (patient 8), neither patient had further episodes of chest pain and were discharged from the hospital receiving the same dose of transdermal nitroglycerin given at the time of their discharge from the coronary care unit. The only change in medical regimen before hospital discharge occurred in patient 4 who had taken atenolol, 50 mg once a day (added empirically to his medical regimen on day 2), despite apparent clinical success with transdermal nitroglycerin alone.

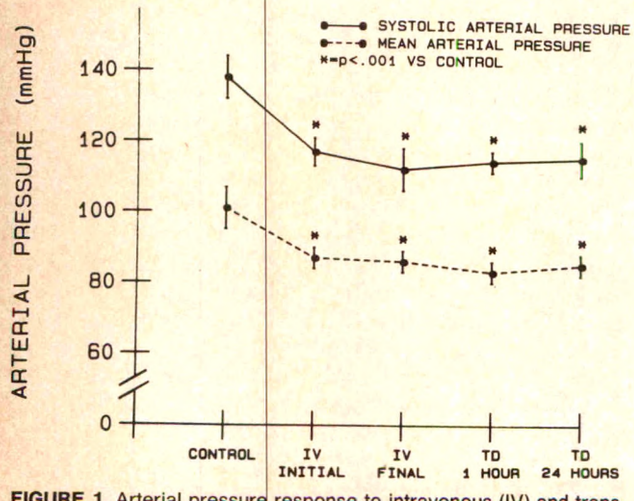

FIGURE 1. Arterial pressure response to intravenous (IV) and transdermal (TD) nitroglycerin. **Solid line** indicates systolic pressure during control period before initiation of IV nitroglycerin. IV final = systolic pressure at the end of the IV infusion just before beginning tapering; IV initial = systolic pressure after initial titration; TD 1 hour = systolic pressure 1 hour after crossover to the TD preparation; TD 24 hours = systolic pressure 24 hours after crossover.

Adverse reactions: In 2 patients, minor adverse reactions were noted during upward titration of the i.v. nitroglycerin infusion. Both had transient hypotension, which was corrected immediately by decreasing the infusion rate; 1 had associated transient sinus bradycardia (54 beats/min).

Methods of data analysis: All data are presented as mean ± standard deviation. Statistical analysis used 2-tailed Student *t* tests for paired values.

Discussion

Intravenous nitroglycerin has been demonstrated to be effective therapy for congestive heart failure complicating AMI,[7] for acute hypertension developing during and after cardiac surgery,[8,9] and for the induction of controlled hypotension during certain surgical procedures.[10,11] Intravenous nitroglycerin is also a valuable addition to our medical management of unstable angina when episodes of chest pain continue to occur at rest despite maximal nonparenteral medical therapy.[3–5] In the present study, all 9 patients entered into the prospective titration protocol and 15 of 17 consecutive patients examined retrospectively became pain free after addition of i.v. nitroglycerin to their prior medical therapy.

The choice of a 10% reduction in mean arterial pressure as the initial titration endpoint was arbitrary, but was the same endpoint that was found to be safe and effective in our recent randomized, placebo-controlled clinical trial of i.v. nitroglycerin treatment in patients with AMI.[12] During previous studies using short-term infusion of i.v. nitroglycerin, invasive hemodynamic monitoring documented that by the time that a 10% reduction in mean arterial pressure had been reached, significant reductions in both left ventricular filling pressure and peripheral vascular resistance had already been achieved.[7,13] Although a 10% reduction in mean arterial pressure was used as the titration endpoint in the present study, it may be more convenient for most coronary care units (in which mean arterial pressure determination must be done manually) to titrate to a 10 to 20% reduction in systolic arterial pressure, depending on the patient's baseline blood pressure.

Three previous studies document the efficacy of i.v. nitroglycerin in unstable angina unresponsive to standard medical therapy. Kaplan et al[4] reported that 25 of 35 patients (71%) became pain free and 8 others (23%) achieved a more than 50% decrease in the number of episodes per day of angina at rest. Success rates of 74 to

86% were reported by Mikolich et al[3] in 47 patients. Curfman et al[5] also observed a significant decrease in the number of pain episodes per day. However, only 5 of 14 patients (36%) became pain free. Curfman's protocol required administration of a dose of β blocker sufficient to reduce heart rate at rest to less than 55 beats/min before the initiation of i.v. nitroglycerin therapy. Beta blockers potentiate coronary vasoconstriction in patients with vasospastic angina, presumably by allowing unopposed α-adrenergic stimulation.[14,15] In the presence of 50% or greater luminal narrowing by a fixed eccentric coronary lesion, even a small change in the remaining circumference of the vessel would result in a marked decrease in blood flow to the region of myocardium supplied by that vessel (i.e., "a dynamic stenosis").[16,17] This discussion is not meant to imply that β blockers may not be beneficial in some subgroups of patients with unstable angina. In a recently completed double-blind randomized placebo controlled trial, Gottlieb et al,[18] at this institution, demonstrated a decrease in the frequency of symptomatic and asymptomatic ischemic episodes with propanolol therapy in patients with unstable angina who were already receiving nitrates and the calcium blocker, nifedipine.

Chierchia et al[19] documented in the catheterization laboratory that the initial abnormality during an episode of angina at rest was a decrease in coronary sinus O_2 saturation, suggesting a decrease in O_2 supply rather than an increase in O_2 demand. Based on these considerations, management of unstable angina should concentrate on pharmacologic therapies that act primarily, although not solely, on the supply side of the myocardial supply/demand equation. Nitrates not only decrease systolic arterial pressure and left ventricular end-diastolic pressure (primary determinants of myocardial oxygen demand), but also dilate large extramural coronary arteries and some eccentric coronary stenoses, thereby potentially increasing myocardial O_2 supply. Nitroglycerin may also improve myocardial O_2 supply by dilating intercoronary collateral channels. By dilating collateral vessels, nitroglycerin could increase blood flow to ischemic regions of myocardium supplied by severely stenosed or even occluded vessels.[20,21] Calcium channel blockers reduce arterial pressure, peripheral vascular resistance and myocardial contractility, which act to reduce myocardial O_2 demand. Like nitrates, calcium channel blockers also act to improve O_2 supply by dilating or preventing vasospasm in large extramural coronary arteries. Beta blockers, in contrast, act primarily on the demand side by decreasing heart rate and contractility, and only secondarily on the supply side by redistributing coronary blood flow to deeper subendocardial layers.[22]

Transcutaneous delivery of nitroglycerin can be accomplished by application of 2% nitroglycerin ointment every 4 to 6 hours for prophylactic treatment of angina. However, nitroglycerin ointment is inconvenient to apply and the surface area of application becomes an important uncontrolled variable. Reichek et al[23] reported that nitroglycerin ointment in doses of 1.5 to 19.0 mg significantly decreases systolic arterial pressure and significantly increases heart rate and exercise duration in patients with stable exertional angina 1 and 3 hours after application. After 2 to 3 months of administration, significant hemodynamic and antiischemic effects could still be demonstrated. Their study design involved progressive dose titration in individual patients.

The new transdermal delivery systems, in addition to being more convenient, precisely control the surface area of skin used for drug delivery. Muller et al[6] reported uniform plasma concentrations of nitroglycerin for 24 hours after application of 1 or more transdermal patches. Hemodynamic effects appeared to be relatively constant between 2 and 10 hours after patch application, with some attenuation or decrease in the magnitude of the hemodynamic effects evident at the end of 24 hours. However, peripheral venous plasma concentrations were low (0.03 to 0.72 ng/ml) when doses of 5 to 20 mg/24 hours were used, compared with 0.1 to 2.24 ng/ml after use of 0.6-mg doses of sublingual nitroglycerin or 12-mg doses of 2% nitroglycerin ointment.[24]

Acute clinical studies testing transdermal nitroglycerin delivery systems in patients with stable angina pectoris generally have revealed improved exercise tolerance 2 to 6 hours after patch application but have yielded conflicting results after 24 hours. Thompson,[25,26] in a double-blind, placebo-controlled, crossover study, using doses of 10 to 20 mg/24 hours, reported significant increases in the duration of exercise after 2 and 26 hours. Hollenberg and Go[27] documented an increase in exercise time to 1 mm of ST-segment depression with 2.5 to 10-mg/24-hour doses of transdermal nitroglycerin, which was comparable to the increase obtained with sublingual nitroglycerin. In contrast, Reichek et al,[28] in a double-blind, placebo controlled trial, reported increased exercise duration 4 and 8 hours after patch application, but minimal effects after 24 hours using "maximally tolerated" transdermal nitroglycerin doses of 20 to 25 mg/24 hours. At smaller doses (mean 9 mg/24 hours) Reichek et al found no significant increase in exercise duration at any time point. However, the presence of other antianginal drugs in most of their patients may have limited the magnitude of benefit obtainable from nitroglycerin alone. Parker and Fung,[29] using doses of 15 to 45 mg/24 hours, showed dose-dependent reductions in systolic blood pressure and increases in exercise duration at 2 and 4 hours, but at 24 hours differences were significant only for the 45-mg/24-hour dose. The need for higher doses was also emphasized by Rajfer et al[30] in a study performed in patients with congestive heart failure. Transdermal nitroglycerin at a mean dose of 26 $\pm$ 3 mg/24 hours reduced left ventricular filling pressure and systemic vascular resistance and increased stroke volume and cardiac index throughout the 24-hour period after patch application.

The present study shows that a wide range of nitroglycerin infusion rates (10 to 200 μg/min) were required to reach the same hemodynamic endpoint in individual patients. Likewise, a wide range of transdermal patch doses (5 to 40 mg/24 hours) were required to accomplish crossover. These findings emphasize the need for individual patient titration and suggest the need for higher dose patches (20 to 40 mg/24 hours) if high-dose transdermal therapy is to be continued chronically.

The present study has at least 2 design limitations. First, the formal crossover study was retrospective. Second, no placebo-treated control group was studied. Although all or part of the clinical improvement could have occurred spontaneously, several admittedly anecdotal observations tend to support a beneficial role of nitroglycerin. The 2 patients in whom transdermal nitrate therapy was either reduced or discontinued immediately had an episode of chest pain at rest. Furthermore, both these patients became pain free when transdermal nitroglycerin treatment was restored to its previous dose. In addition, the 2 patients who had an episode of chest pain during the first 24 hours after crossover had no further chest pain after their transdermal dose was increased by 10 mg/24 hours. Finally, this short-term study does not consider the issue of hemodynamic attenuation. Whether higher transdermal doses and/or a nitrate-free period will be necessary to optimize antianginal effects during long-term therapy awaits the results of ongoing clinical trials.

In summary, the results of the present study, while not ruling out the possibility of spontaneous improvement, do suggest that the addition of i.v. nitroglycerin to prior oral antianginal therapy, followed by crossover to transdermal nitroglycerin, is a safe and effective means of managing patients with unstable angina.

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Ischemia During Angioplasty After Streptokinase: A Marker of Myocardial Salvage

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Although thrombolytic therapy can result in lysis of a coronary artery thrombus, salvage of myocardium as measured by enzymatic, electrocardiographic and regional wall motion evaluation has not been clearly documented. Many patients after successful reperfusion continue to experience recurrent chest pain. The presence of recurrent chest pain suggests salvaged myocardium. Controlled reocclusion of the infarct vessel with the use of coronary angioplasty may support evidence for myocardial salvage. Experience in 50 patients who underwent angioplasty was reviewed retrospectively. Sixteen of the 50 patients had electrocardiographic or clinical evidence of ischemia at the time of balloon inflation. Prospectively, all patients who underwent angioplasty after they had received streptokinase were evaluated, and 5 of 5 patients had chest pain and ST-segment elevation during balloon inflation. The development of ischemic changes during balloon catheter inflation suggests the presence of persistently viable, salvaged myocardium after successful thrombolysis. (Am J Cardiol 1985;56:749–752)

Potential myocardial salvage as a result of thrombolytic therapy during acute myocardial infarction (AMI) has not been proved. Improvements in regional and global function have been inconsistent.[1–4] Nevertheless, many patients have recurrent chest pain after successful thrombolysis.[5] Ischemic pain is presumably a result of transient reocclusion of the infarct-related vessel, suggesting residual viable myocardium. Rather than evaluating the effects of spontaneous transient reocclusion, a more precise method for detecting viable myocardium would be controlled reocclusion of the infarct-related vessel accomplished during coronary angioplasty. The development of electrocardiographic (ECG) changes or chest pain during angioplasty balloon inflation was retrospectively analyzed in patients recently treated with intracoronary or intravenous streptokinase (SK) for an AMI. Then, ischemic manifestations during angioplasty were prospectively evaluated in all subsequent patients receiving intravenous SK for AMI.

Methods

During an 18-month period, 130 patients with AMI received SK: 87 received intracoronary SK, 36 received intravenous SK and 7 received intravenous followed by intracoronary SK. Criteria for the infusion of SK included: age younger than 70 years; chest pain less than 12 hours in duration; and more than 1.0 mm of ST elevation, suggestive of transmural injury. In patients receiving intravenous SK who had persistent chest pain 90 minutes after infusion, emergency angiography was performed to assess vessel patency and intracoronary SK was infused if the infarct vessel was occluded. Myocardial necrosis was confirmed by elevation of creatine kinase isoenzyme levels in all patients. Fifty patients had coronary angioplasty performed 30 minutes to 72 hours after SK administration for: recurrent chest pain and ECG changes in the distribution of the infarct vessel; and/or greater than 70% residual stenosis of the infarct vessel. During intravenous nitroglycerin infusion, at least 3 inflation-deflation dilatation sequences were completed, ranging from 30 to 90 seconds. The minimal peak inflation pressure was 2 atmospheres higher than the balloon indentation resolution pressure. Side branch occlusion was not noted during or after angioplasty. New evidence for myocardial ischemia during angioplasty was considered to be chest pain during balloon inflation similar to previous pain of infarction or ECG changes during balloon inflation, consisting of ST elevation or depression. (The electrocardiogram was typically a single channel, recording only lead 2 or lead 3.)

Prospectively, all subsequent patients who received intravenous SK were evaluated by determining if the same markers for ischemia were present during angioplasty. Five of the next 7 sequential patients who received intravenous SK with clinical evidence for reperfusion had patent infarct-related vessels and underwent successful angioplasty.

Left ventricular wall motion abnormalities were evaluated by subjective assessment of the single-plane (45° right anterior oblique) or biplane contrast (45° right anterior oblique/25° cranial–60° left anterior oblique) ventriculograms, except in 2 patients who had nuclear ventriculograms because of clinical instability.

Results

Sixteen of the 50 patients who underwent angioplasty had chest pain or ischemic ECG changes during balloon

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TABLE I Retrospective Evaluation of Patients Undergoing Transluminal Coronary Angioplasty After Streptokinase Administration

Pt	Route	IRV	Coll	Time (min)	% Sten Pre-SK	% Sten Post-SK	% Sten Post-TCA	LVEF (%)	WMA	CP	ECG
1	IC	Right	0	60	90	90	100	39	Ak:PB,D Hk:A	0	Minor ST V Occl
2	IC	LC	0	360	90	90	40	58	Hk:AL,IL,PL	+	ST↑
3	IC	LAD	0	180	80	80	30	65	Dk:A Ak:AL	0	ST↓
4	IC	Right	0	360	90	70	20	46	AK:PB,D,IL,PL	0	ST↑
5	IC	Right	+	120	100	70	50	64	Hk:PB	Resolved w/TCA	No
6	IV-IC	LAD	+	510	100	80	30	47	Dk:A,AL	+	ST↑
7	IV-IC	Right	+	1,400	100	60	20	51	Dk:A Hk:PB,D	+	ST↑
8	IC	Right	0	330	70	50	50	56	Ak:D	+	ST↑
9	IV	LAD	0	150	. . .	70	0	43	Ak:AL,A	0	ST↓
10	IV	LAD	0	. . .	. . .	90	30	61	Ak:A,S Hk:AL	0	ST↓
11	IV	Right	+	150	. . .	90	20	80	0	+	ST↑
12	IV	Right	0	45	. . .	90	20	81	0	+	ST↑
13	NTG	Right	0	270	100	90	50	57	Hk:PB,D	Resolved w/TCA	No
14	IC	Right	0	270	100	70	40	48	Ak:PB,D	+	No
15	IC	LAD	0	180	100	90	30	58	Ak:AL Hk:A	0	ST↑
16	IC	LAD	0	120	100	80	30	37	Ak:AL Hk:A,D	0	ST↑

A = apical; Ak = akinesia; AL = anterolateral; Coll = collaterals; CP = chest pain; D = diaphragmatic; DK = dyskinesia; ECG = electrocardiogram; HK = hypokinesia; IC = intracoronary; IL = inferolateral; IRV = infarct-related vessel; IV = intravenous; LAD = left anterior descending coronary artery; LC = left circumflex artery; LVEF = left ventricular ejection fraction; PB = posterobasal; PL = posterolateral; Right = right coronary artery; S = septal; SK = streptokinase; SL = superolateral; Sten = stenosis; TCA = transluminal coronary angioplasty; V = vessel; WMA = wall motion abnormality; + = present; 0 = absent; ↑ = elevation; ↓ = depression.

TABLE II Prospective Evaluation of Patients Undergoing Transluminal Coronary Angioplasty After Streptokinase Administration

Pt	Route	IRV	Coll	Time (min)	% Sten Pre-SK	% Sten Post-SK	% Sten Post-TCA	LVEF (%)	WMA	CP	ECG
1	IV-IC	LAD	0	360	100	90	20	29*	Ak:AL H:S Dk:A*	+	ST↑
2	IV	Right	0	90	. . .	60	20	50	Hk:PB,PL Ak:D	+	ST↑
3	IV	LC	0	150	. . .	80	40	44	Ak:PB, IL,PL Hk:D,SL	+	ST↑
4	IV	Right	0	300	. . .	90	40	55*	Hk:PL*	+	ST↑
5	IV	LAD	0	120	. . .	70	50	31	Dk:AL,A Ak:S	+	ST↑

* Obtained by nuclear ventriculogram owing to clinical instability.
Abbreviations as in Table I.

inflation (Table I). The infarct-related vessel was the left anterior descending artery in 6 patients (38%), the right coronary artery in 9 patients (56%) and the left circumflex in 1 patient (6%). Collaterals to the infarct-related vessel were noted in 4 (25%). The average duration of chest pain before intervention was 300 ± 330 minutes. The average global ejection fraction for the group was 56 ± 13%. Wall motion abnormalities were identified in 88% of the patients: 40% had akinesia or dyskinesia in the infarct-related zones, 24% had both akinesia and hypokinesia in the infarct-related zones, 24% had hypokinesia alone in the infarct-related segments, and 12% had no wall motion abnormalities.

During balloon inflation, 1 patient had chest pain only, 6 patients had ECG changes only and 6 had both chest pain and ECG changes. In 1 patient, balloon inflation resulted in occlusion of the infarct vessel with the development of ST changes but no pain. Two other patients had marked chest pain before angioplasty, but after balloon inflation, which resulted in an improvement in anterograde flow, chest pain rapidly resolved (Table I). Typical ECG changes during balloon inflation are shown in Figure 1.

Five sequential patients underwent coronary angioplasty 48 hours after intravenous SK administration (Table II). All showed wall motion abnormalities in the distribution of the infarct-related artery. All patients had chest pain and ST-segment elevation during balloon inflation. Thus, balloon occlusion of the infarct-related vessel produced or relieved myocardial ischemia in 21 of 55 post-AMI patients.

Discussion

The goal of aggressive treatment in AMI is to decrease infarct size by limiting necrosis. Thrombolytic treatment for AMI has not clearly resulted in a reduction in

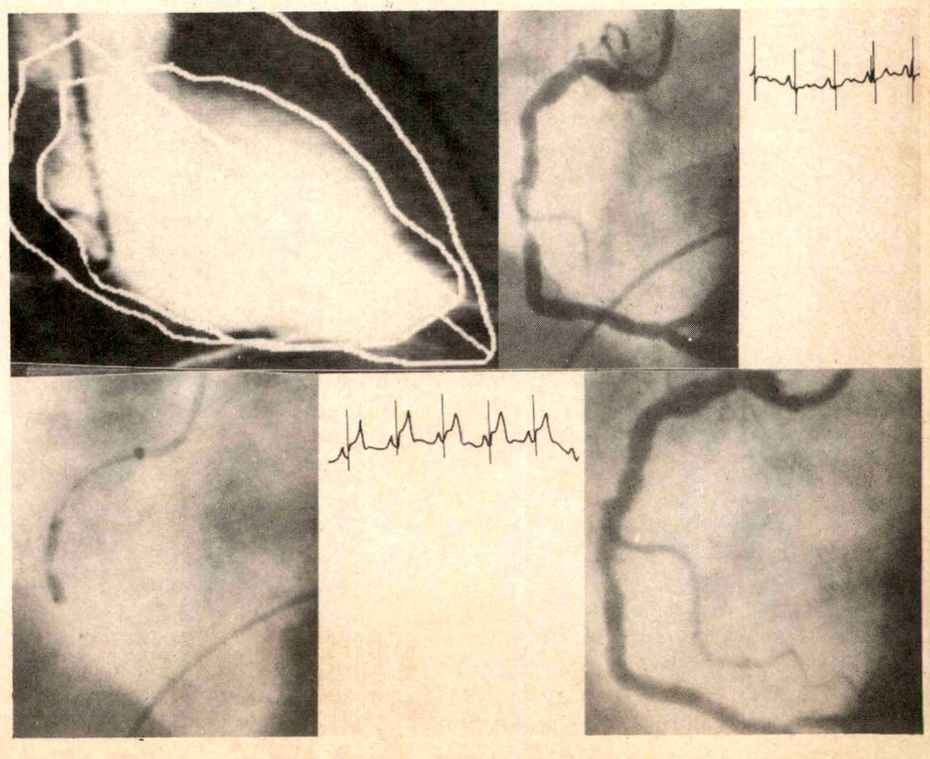

FIGURE 1. Top left, ventriculogram of study patient 48 hours after intravenous streptokinase administration showing akinesia in the diaphragmatic segment and hypokinesia in posterobasal segment. Top right, angiogram of the right coronary artery with a 70% midstenosis 48 hours after infusion of intravenous streptokinase. The simultaneous electrocardiogram is shown. **Bottom left,** coronary angioplasty balloon inflated in the right coronary artery. Patient had marked ST elevation and chest pain. **Bottom right,** final angiographic result after angioplasty.

the area of necrosis.[1–4] Inherent problems with the techniques for assessing infarct size, however, make determination of reduction difficult. Creatine kinase–MB isoenzymes cannot be used to estimate the extent of myocardial necrosis,[6–8] because reperfusion results in "washout" of enzymes from necrotic areas so that the relation between infarct size and enzyme levels is not proportional. Electrocardiographic mapping is limited in that it can be applied only in anterior or lateral infarcts,[9,10] and the absolute height of the ST segment is affected by intraventricular conduction defects, artificial pacemakers, pericarditis, chest wall thickness and intervening lung tissue.[11] Finally, measurements of regional wall motion to assess infarct size are limited by the inability to differentiate infarction from ischemia. In addition, there is often a lagging return of mechanical function even when reperfusion involves reversibly injured myocardium, a condition referred to as "stunning" of the myocardium.[12,13]

Clinical myocardial ischemia is characterized by the development of chest pain and confirmed by ECG, hemodynamic and wall motion abnormalities, which return to normal after the ischemic episode. If reperfusion of infarcted myocardium salvages tissue, then subsequent transient interruption of coronary flow at the same anatomic site should produce ischemia manifested by chest pain or ECG changes. This is supported by recurrent episodes of clinical ischemia observed in patients after SK administration.

The present study was undertaken to examine the effects of transient balloon occlusion of coronary blood flow at the stenotic site after thrombolysis to detect the presence of viable myocardium in the previous area of myocardial infarction. Myocardial ischemia was documented in 14 patients undergoing angioplasty during balloon inflation. Transient reocclusion resulting in myocardial ischemia can only indicate the presence of preserved viable myocardium. In 2 other patients, ischemia was resolved with improvement in anterograde flow as a result of successful angioplasty.

The actual percentage of patients with ischemia at the time of angioplasty may be higher than the initial 32% (16 of 50) documented by retrospective review because (1) ECG changes and chest pain at the time of angioplasty were not systematically recorded; (2) monitoring of the electrocardiogram was predominantly in leads 2 or 3, which would have resulted in underestimation of ischemic changes in balloon inflation in the left anterior descending artery; (3) all patients were receiving nitroglycerin at the time of infusion, which decreases the potential for provoking ischemia; (4) the duration of balloon inflation was variable, and more prolonged inflation could have precipitated ischemia; and (5) collateral flow can attenuate ischemia and again decrease the potential for provoking ischemia. Prospective evaluation of 5 patients who had successful coronary angioplasty, however, revealed both chest pain and ST changes compatible with ischemia at the time of balloon inflation.

The major limitation of the investigation concerns the patients in whom a subtotal occlusion was identified before the administration of SK, and the group of patients who received intravenous SK, where infarct vessel patency was not initially angiographically identified. Although one may conclude that SK can result in no benefit to patients with subtotally occluded vessels, continued transient or even complete reocclusion of the vessel may occur,[14] and establishment of a lytic state may be important in maintaining vessel patency to preserve left ventricular function. In the patients receiving intravenous SK in which initial infarct vessel patency was not angiographically identified, we have used the standard clinical criterion for identifying successful lysis: resolution of chest pain shortly after infusion of the agent.[15–17] In patients with persistent chest pain, emergency catheterization was performed to evaluate the infarct vessel, at which time intracoronary SK was administered if there was occlusion. Hence, we believed that SK therapy was important in either initiating or maintaining infarct vessel patency in all patients.

Although the methods of assessing salvage after reperfusion have limitations, the presence of recurrent ischemic events after successful thrombolysis suggests viable myocardium. Although major left ventricular wall motion abnormalities persist, recurrent ischemia during angioplasty after SK administration in a significant number of patients supports the concept of preserved viable myocardium.

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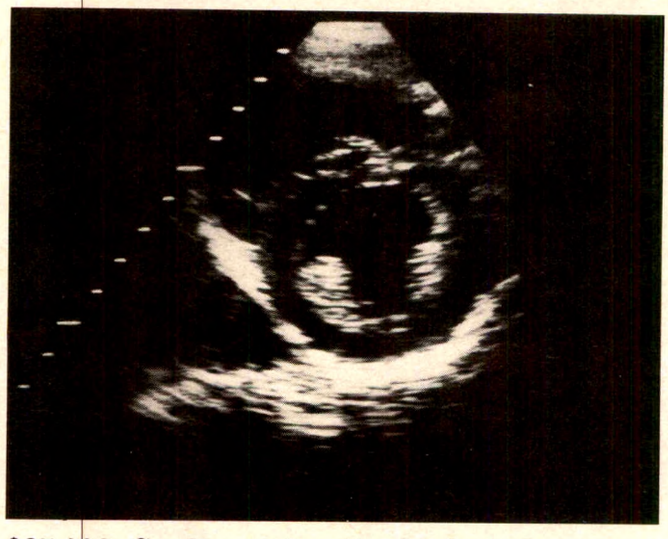

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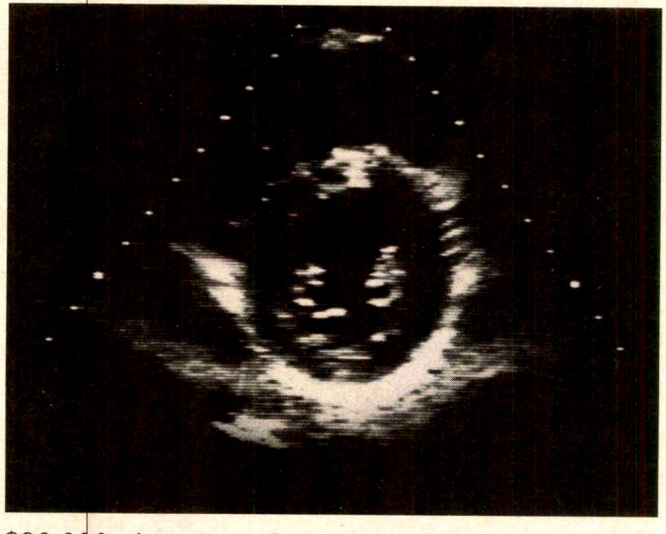

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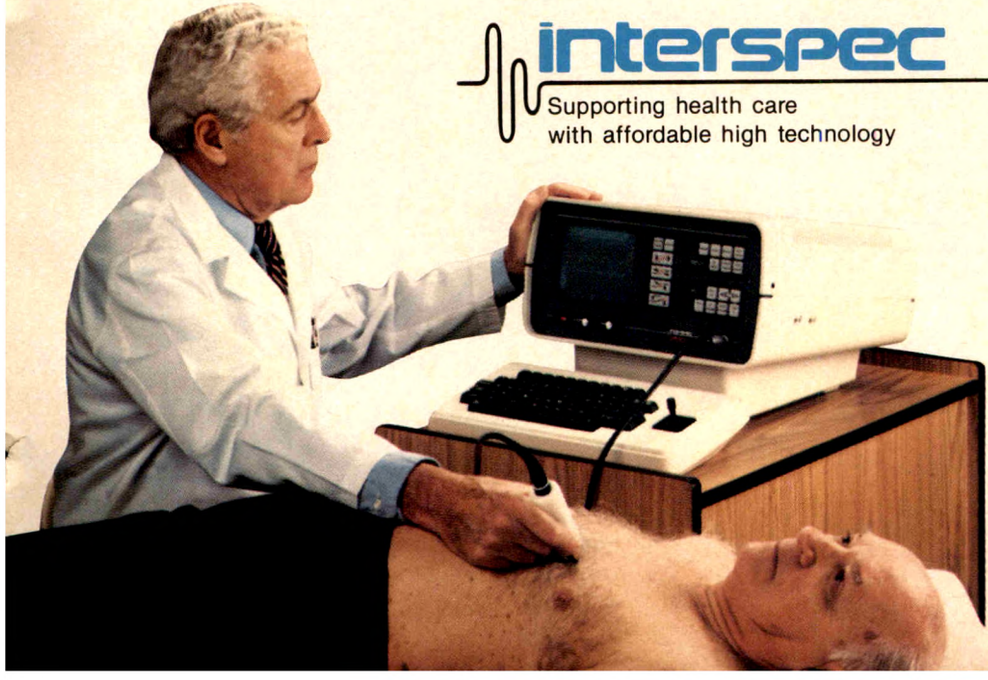

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If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.
Patients should always be started on the 1 mg capsule of MINIPRESS. The 2 and 5 mg capsules are not indicated for initial therapy.
More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.
Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS in pregnancy has not been established. MINIPRESS is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of MINIPRESS in children.
ADVERSE REACTIONS: The most common reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.
The following reactions have been associated with MINIPRESS some of them rarely. (In some instances exact causal relationships have not been established.)
Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus, alopecia, lichen planus.
Genitourinary: urinary frequency, incontinence, impotence, priapism.
EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.
Other: diaphoresis.
Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances the exact causal relationship has not been established because the baseline observations were frequently inadequate.
In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.
DOSAGE AND ADMINISTRATION: The dose of MINIPRESS should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:
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Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.
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More detailed information available on request.

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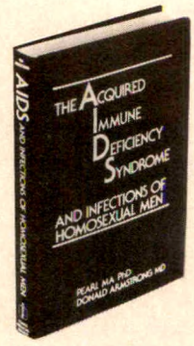

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Evaluation of Methods of Measurement and Estimation of Left Ventricular Function After Acute Myocardial Infarction

MICHAEL G. JONES, BA, BARRY W. RAMO, MD, GILBERT L. RAFF, MD, TOMOAKI HINOHARA, MD, and GALEN S. WAGNER, MD

Using multiple gated cardiac blood pool imaging and single-plane ventriculography from cardiac catheterization, 2 independent measures of left ventricular (LV) ejection fraction (EF) were determined in each of 21 patients. Patients were seen 2 to 6 weeks after their first acute myocardial infarction and were free of electrocardiographic evidence of conduction abnormalities and left or right ventricular hypertrophy. Differences between the 2 measures of LVEF were examined and then compared with the extent of myocardial necrosis estimated from the standard 12-lead electrocardiogram using the complete 54-criteria/32-point Selvester QRS scoring system. Regression analysis yielded an r value of 0.81 (SEE = 8.05) for the overall relation between the 2 measures of LVEF. Correlation coefficients of −0.70, −0.66 and −0.72 were obtained for the relations of radionuclide LVEF, catheterization LVEF and the mean of these 2 determinations, respectively, compared with QRS score. A QRS score 4 or less achieved 100% specificity and that of 8 or less 100% sensitivity for predicting an LVEF greater than 40%. Thus, the Selvester QRS scoring system may be of value in identifying patients with or without markedly impaired LVEF. This risk stratification may be important in reaching optimal postinfarction therapeutic decisions.

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Left ventricular (LV) ejection fraction (EF) is often used as an estimation of LV function and subsequent prognosis after acute myocardial infarction (AMI). Radionuclide and contrast ventriculography are the methods most often used for measuring LVEF and intertechnique correlations have consistently been good in patients without AMI.[1–3] However, comparison of LVEF in the immediate post-AMI period measured by both radionuclide and contrast ventriculography has not been reported. The Selvester QRS scoring system, which is based on the standard 12-lead electrocardiogram (ECG), has been shown to correlate significantly with AMI size,[4–6] and formulas have been developed to describe the relation of QRS score to postinfarction LVEF.[7–13] Some of these studies have used radionuclide angiography[9–12,14] and others, contrast ventriculography[8,15] as their standard for evaluating other techniques. In this study, the Selvester QRS scoring system was applied to each patient's 12-lead ECG. Correlations were made between the 2 methods of LVEF measurement, the QRS score and each of the methods for determining LVEF, and the QRS score and the mean of the 2 LVEF values.

From the Department of Medicine, Duke University Medical Center, Durham, North Carolina, and the Presbyterian Heart Institute, Presbyterian Hospital Center, Albuquerque, New Mexico. This work was supported in part by Research Grant HL-17670 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received March 12, 1985; revised manuscript received May 20, 1985, accepted May 22, 1985.

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Methods

Study population: Patients were referred for cardiac catheterization 2 to 6 weeks (mean 3.75) after their first AMI, which occurred between July 1982, and March 1984. Infarction was documented by patient history, ECG and enzyme studies; catheterization was performed to evaluate the severity of coronary artery disease and ventricular dysfunction. Patients were required to meet the following inclusion criteria: a standard 12-lead ECG taken 24 to 36 hours before cardiac catheterization; a multiple-gated cardiac blood pool scan performed within 48 hours of catheterization; no associated valvular heart disease; no evidence on ECG of left or right ventricular hypertrophy, left anterior or posterior fascicular block or left or right bundle branch block; and no antiarrhythmic medication for frequent premature ventricular contractions, atrial fibrillation or ventricular tachycardia. Twenty-one patients (19 men, 2 women) met inclusion criteria for this study (Table I). Mean age was 58 years (range 39 to 71).

Gated blood pool study: A multiple-gated blood pool study was performed to measure the radionuclide LVEF within 48 hours of cardiac catheterization in all 21 patients. Sixteen patients had their radionuclide study within 24 hours before catheterization; in the other 5, it was performed within 48 hours after catheterization.

After red blood cell tagging with pyrophosphate, the modified in vitro method was used for the administration of 20 to 24 mCi of technetium-99m sodium pertechnetate. The patient was positioned and imaged for an anterior, best septal (left anterior oblique) and steep left anterior oblique 70° views. Each projection was acquired via computer (ADAC CDS) for 6 minutes in a dynamic 64 × 64 × 8 mode in 16 segments. Areas of interest from end systole, end diastole and an apical background region were determined using an automatic edge-detection program. These areas were visually checked

TABLE I Demographic Data of 21 Patients

Pt	AMI Location	Age (yr) & Sex	Vessels ≥75% Occluded	QRS Score	RN LVEF (%)	Cath LVEF (%)	Mean LVEF (%)
A1	Lat	64M	0	0	57	56	57
A2	Lat	63M	1	2	37	46	42
A3	Ant	56F	2	6	49	47	48
A4	Ant	66M	2	12	38	42	40
A5	Ant	40M	2	13	27	29	28
A6	Ant	52M	2	0	65	68	67
A7	Ant	61M	2	3	62	58	60
A8	Ant	66F	2	2	44	67	56
A9	Ant	71M	3	6	22	30	26
A10	Ant	63M	1	5	62	57	60
A11	Ant	52M	1	3	54	59	57
I1	Inf	56M	1	13	36	40	38
I2	Inf	61M	2	0	61	53	57
I3	Inf	55M	2	2	66	62	64
I4	Inf	64M	2	10	30	34	32
I5	Inf	61M	3	1	62	44	53
I6	Inf	51M	2	5	38	33	36
I7	Inf	61M	2	8	43	45	44
I8	Inf	65M	2	1	56	57	57
I9	Inf	44M	1	8	43	48	46
I10	Inf	39M	2	7	43	47	45

Ant = anterior; AMI = acute myocardial infarction; Cath = catheterization; Inf = inferior; Lat = lateral; LVEF = left ventricular ejection fraction; RN = radionuclide.

for accuracy, with manual correction if necessary, and a global radionuclide LVEF was determined using the aforementioned program.

Cardiac catheterization: Patients underwent catheterization from either the femoral or brachial artery approach within 36 hours of their admission ECG. Single plane contrast ventriculography was performed to obtain the "catheterization LVEF" before selective coronary angiography. Ventriculography was accomplished in the 30° right anterior oblique position using 40 to 60 ml of contrast medium over 2 to 3 seconds. Tracings of the left ventricle in peak systole and diastole were manually drawn and subsequently digitized to estimate LVEF according to a standard technique.[16] The degree of stenosis in each of the major coronary arteries was visually assessed and a "diseased vessel" was defined as one with 75% or more narrowing.

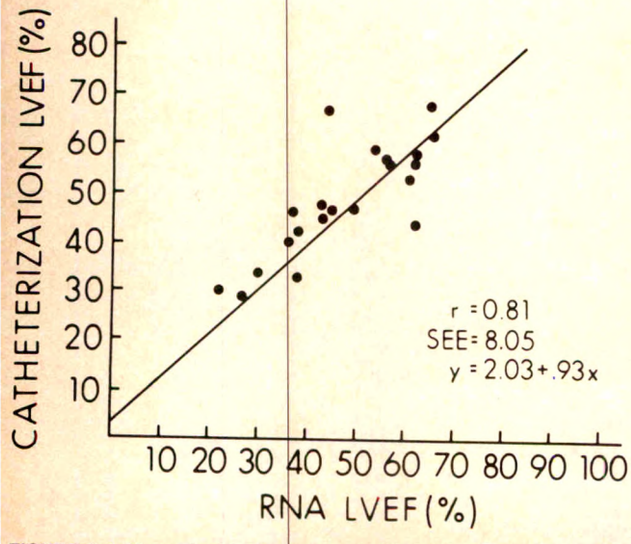

FIGURE 1. Left ventricular ejection fraction (LVEF) correlation between catheterization contrast ventriculography and multiple gated cardiac blood pool imaging (RNA) in 21 patients evaluated 2 to 6 weeks after acute myocardial infarction.

QRS scoring system: A point score was determined from each patient's ECG using the complete 54-criteria/32-point QRS scoring system developed by Selvester et al[17–19] and refined for specificity and application by Hindman et al.[20] ECGs were independently scored by 2 trained observers and discrepancies resolved by conference.

Statistical analysis: Analyses were performed using the Student *t* test, analysis of variance or both. Correlations between LVEF measurements and QRS scores were assessed with linear regression analysis. The mean value of LVEF was determined as ½(radionuclide LVEF + catheterization LVEF). Values were expressed as the mean ± standard deviation. A mean LVEF of more than 40% was selected for assessing specificity and sensitivity of the various levels of QRS score because values of 40% or less are considered indicative of marked impairment of LV function.

Results

Of the 21 patients studied, 10 had inferior AMI, 9 had anterior AMI and 2 had lateral AMI. Four infarcts were subendocardial (non-Q-wave). The mean QRS score was 5.1 ± 4.3 points (range 0 to 13). No significant difference was noted between the number of QRS points scored by patients with anterior AMI (mean 5.5 ± 4.3) vs inferior AMI (mean 5.6 ± 4.4). Table I lists the demographic data for these 21 patients.

Figure 1 displays the regression analysis between radionuclide and catheterization LVEF. Mean LVEF from catherization was 49 ± 12% (range 29 to 68) and 47 ± 13% (range 22 to 66) from radionuclide study; regression analysis yielded an r value of 0.81 (SEE = 8.05) between these parameters. In 13 of the 21 patients (62%) the radionuclide LVEF was less than the catherization LVEF by an average of 5.6%; in 8 patients, radionuclide LVEF averaged 5.8% more than catherization LVEF. In only 5 of the 21 patients was the difference between methods 5% or more.

Figure 2A depicts the relation of QRS score to radionuclide LVEF. The correlation coefficient was −0.70 (SEE = 9.78). The correlation coefficient for catheter-

ization LVEF vs QRS score was −0.66 (SEE = 8.92) (Fig. 2B). Further analysis between the mean value of both measures of LVEF and the QRS score yielded a correlation coefficient of −0.72 (SEE = 8.49). This relation was not significantly different from that of each method considered independently.

Figure 3 depicts the sensitivities and specificities attained by the various levels of QRS scores for identifying patients with a mean LVEF of more than 40%. A QRS score of 4 points or less achieved 100% specificity and that of ≤8 points 100% sensitivity for predicting an LVEF >40%. QRS scores of 5, 6 and 7 were associated with both levels (≤40% and >40%) of LVEF.

Discussion

In this study the relation of the Selvester QRS score to both radionuclide LVEF obtained via multiple gated blood pool imaging and catheterization LVEF obtained via contrast ventriculography was evaluated. The QRS scoring system has been reported in a simplified 37-criteria/29-point version[21] and, recently, in its complete 54-criteria/32-point form.[20] Previous studies have examined the relation of the simplified system to thallium-201 scintigraphy,[9,11] radionuclide left ventriculography[7,9,11,12,14] and clinical, angiographic and prognostic measures.[8,15,22] This study was unique because it examined the relation of the complete version of the scoring system to both radionuclide and catheterization LVEF performed in a group of patients with AMI.

Previous studies examining the relation of radionuclide to catheterization measures of LVEF in non-AMI patients have yielded r values ranging from 0.80 to 0.97 for first-pass techniques,[23] and values as high as 0.93 using computer-generated time-activity curves.[1,3,24] Correlation coefficients have ranged from 0.80 to 0.95 for LVEF comparisons between single plane ventriculography and radionuclide techniques in non-AMI patients.[2,3] No previous study has evaluated this relation in patients immediately after AMI. The correlation coefficient of 0.81 for post-AMI patients in the present study is at the low end of the reported range. However, no systematic difference was noted between the techniques in the measurement of LVEF.

The relation between radionuclide and catheterization LVEF in AMI patients might differ from that for non-AMI patients because the manifestation of and subsequent recovery from AMI varies in individual patients. Dyssynergic or asynergic regions, depending on their location or severity, might distort one measure of LVEF, thus weakening the correlation established in non-AMI patients. Limitations of the techniques used to measure LVEF might under- or overestimate the amount of necrosis responsible for decreased ventricular function. Thus, it was hypothesized that the mean of the 2 techniques would yield a more accurate measure of each patient's true LVEF. However, the regression analysis of mean LVEF vs QRS score showed a relation not significantly different from that when each parameter was considered independently.

Comparison of QRS score to both radionuclide and catheterization LVEF (Fig. 2) yielded correlation coefficients consistent with previously reported values.[7–11,15] Scatter about the low-QRS score end of these regression lines would be expected because of normal compensational variability in hearts with minimal

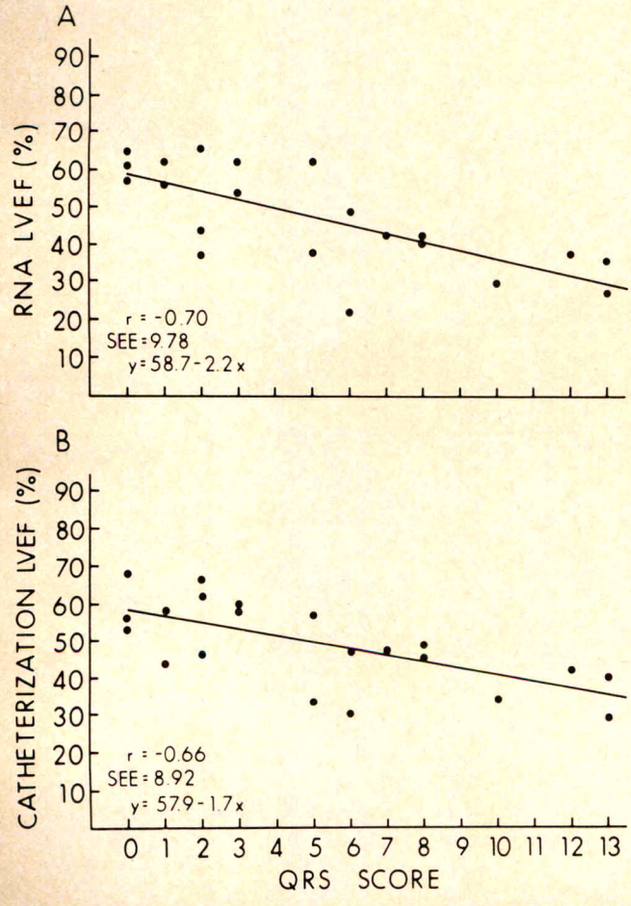

FIGURE 2. Correlations between the QRS score from the 12-lead electrocardiogram and both measures of left ventricular ejection fraction (LVEF). **A,** relation of QRS score and LVEF as determined by multiple gated cardiac blood pool imaging (RNA). **B,** relation of QRS score and LVEF from catheterization single-plane ventriculography.

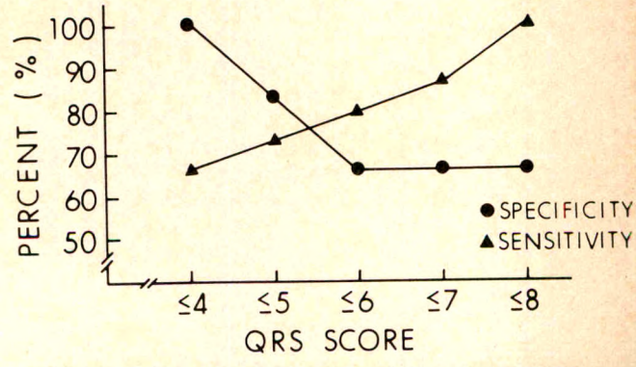

FIGURE 3. Spectrum of specificities and sensitivities per QRS score for indicating patients with a mean left ventricular ejection fraction (½[radionuclide + catheterization]) of more than 40%. Values of specificity and sensitivity are given for each QRS score. The circle corresponding to a QRS score of ≤5 points, for example, represents a specificity of 83%, indicating that 17% of patients (1 of 6) with an LVEF of 40% or less will be falsely included. Similarly, the triangle corresponding to the same score represents a sensitivity of 73%, indicating that 27% of patients (4 of 15) with LVEF of more than 40% will be falsely excluded.

ventricular necrosis. In patients with a low QRS score and depressed ventricular function, some degree of dysfunction may be attributed to residual myocardial ischemia. A study recently completed at this institution,[13] comparing radionuclide LVEF to a QRS score, predicted LVEF in patients before and after coronary artery bypass grafting to identify the cause of depressed LV function. In that study, Hinohara et al conclude that depressed LVEF is due not only to previous AMI, but also to ischemia, which may be reversed by coronary artery bypass surgery. DePace et al[11] have noted that ischemia at rest may limit the usefulness of the ECG to assess LVEF in the individual patient. Thus, in patients with diminished LVEF and a low QRS score, indicative of minimal myocardial necrosis, further intervention may be beneficial in improving ventricular performance and, subsequently, survival after AMI.

Several studies have evaluated the relation between measured LVEF and that estimated by the Selvester QRS scoring system after AMI. Young et al[10] reported that a low QRS score did not reliably predict a normal LVEF in patients with prior AMI; however, they used the simplified version of the scoring system and defined a normal LVEF as ≥50%. Roubin et al,[8] using the simplified system, subsequently determined that a QRS score ≥7 had a specificity of 97% and a sensitivity of 59% for predicting a catheterization LVEF <45%. DePace et al[11] then described a group of 48 patients who were evaluated 2 weeks after AMI; all patients with a QRS score ≤3 had a radionuclide LVEF >40%.

An LVEF of 40% or less is commonly believed to be indicative of marked impairment of LV function and is taken into consideration when reaching decisions regarding prognosis and therapy. Thus, it would be useful to have a quick, inexpensive and readily available method for identifying patients with an LVEF above and below this 40% level. In this study, a QRS score of 4 or less was required to exclude all 6 patients with a mean LVEF of 40% or less (100% specificity), while a score of 8 points or less was required to include all 15 patients with a mean LVEF >40% (100% sensitivity). Thus, it appears the Selvester QRS scoring system is an effective method for identifying patients with or without diminished LVEF after AMI. Because the number of patients in this study was relatively small, these results require validation in future studies.

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Infections in a Coronary Care Unit

WINSTON A. SCHANDORF, MD, RICHARD B. BROWN, MD, MICHAEL SANDS, MD, and DAVID HOSMER, PhD

All infections in patients in an active coronary care unit (CCU) over a 3-year period were analyzed to ascertain rates, outcomes, pathogens and sites of infections. Standard surveillance methods and definitions of the Center for Disease Control were used. A total of 236 infections were documented in 200 infected patients. Infection rates were 5 and 2% for total and CCU-acquired infections, respectively. CCU infections accounted for 11% of nosocomial infections that occurred within all critical care areas surveyed. Of all documented infections, 131 (56%) were community-acquired and 90 (38%) were acquired within the CCU. Lower respiratory and urinary tract infections were most frequently noted, with *E. coli*, *S. aureus*, and klebsiella-enterobacter-serratia most usually implicated. Mortality among patients with infections was 31%, compared with 8 to 12% in those who were not infected. Those with lower respiratory infections or primary bacteremias had a higher mortality rate than those with infections at other sites ($p < 0.001$). Infections are seen in close to 5% of CCU patients and may adversely affect the survival rate. The mortality rate in infected patients may be 3 times higher than that in the general CCU population. This study also provides data against which other similar institutions can gauge their CCU infection rates.

(Am J Cardiol 1985;56:757–759)

In at least 5% of hospitalized patients within the United States, nosocomial infections develop.[1–5] However, the incidence of nosocomial infection in patients in medical/surgical intensive care units may be significantly greater than this, rates in excess of 20% have been reported.[6,7] Many of these infections are device-related and may be prevented with appropriate infection control measures.[3,8–10]

Studies of infection in the coronary care unit (CCU) are imprecise. A recent statewide study revealed a rate of nosocomial infection of only 1 to 2% within 13 CCUs that were surveyed.[1] However, data collection was incomplete and information concerning pathogens, survivorship and sites of infection was lacking. The present study reviews all infections that occurred in an active CCU during the 3 years between 1982 and 1984 with regard to origin of infection, outcome status, and both the sites and pathogens implicated. This information is important in defining an area for potential reduction of CCU morbidity and mortality and is a yardstick against which other CCUs can gauge their own infection rates for quality assurance purposes.

Methods

The Baystate Medical Center is a 950-bed teaching community hospital associated with the Tufts University School of Medicine. The institution is the second largest hospital in Massachusetts, and admits approximately 40,000 patients yearly for a mean stay of 8 days. Five critical care areas account for 62 beds (7% of total). The CCU contains 16 beds (26% of total critical care beds), all of which are located in private rooms. Criteria for admission to the CCU include documented or suspected mycardial infarction, unstable angina, severe arrhythmias and cardiogenic shock.

The surveillance methods used in our study conformed with those recommended by the Centers for Disease Control.[11] Trained infection control personnel prospectively surveyed all critical care areas on a daily basis and documented infections by using standard surveillance methods. Data recorded included usual demographic characteristics, sites of infection, pathogens implicated and location where the infection was acquired. Infection data were obtained from the patient charts, radiology reports and microbiology results. Infections were defined as community-acquired if infection became clinically manifest before or within 48 hours of hospitalization, as CCU-acquired if they developed more than 48 hours after admission to the CCU or less than 48 hours after CCU discharge, or as other nosocomial if they developed more than 48 hours after hospitalization but not in the CCU.

The following criteria were used for diagnosing infection: (1) Lower respiratory infections were identified by the presence of purulent sputum, fever and cough plus a chest x-ray demonstrating new alveolar infiltrates. (2) Urinary tract infections were identified by significant bacteriuria (more than 10^5 organisms/ml of urine) regardless of symptoms. (3) Wound infections were identified by purulent drainage. (4) Other cutaneous sources (cellulitis, furuncles) were diagnosed by usual clinical criteria. (5) Bacteremias required the documentation of the same organism in at least 2 separate blood cultures. (6) Meningitis required a positive cerebral spinal fluid culture or gram stain. All infected patients were followed up until either death or hospital discharge to determine their clinical outcome status (i.e., lived to hospital discharge, died in CCU or died after CCU discharge). The total number of

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TABLE I Comparative Numbers and Rates of Infection and Other Characteristics of Intensive Care Units (ICU) Studied

ICU Type	No. of Admissions (%)	No. of Beds (%)	Number of Infections			Infection Rates*		
			Total (%)	ICU-Acq. (%)	Comm-Acq. (%)	Total	ICU-Acq.	Comm-Acq.
Med/surg	5,189 (36)	22 (35)	1,217 (66)	581 (68)	463 (60)	24	11	9
Coronary	5,017 (35)	16 (26)	236 (13)	90 (11)	131 (17)	5	2	3
Pediatric	965 (7)	6 (10)	221 (12)	60 (7)	155 (20)	23	6	16
Neonatal	1,848 (13)	14 (23)	152 (8)	109 (13)	25 (3)	8	6	1
Card surg	1,341 (9)	4 (6)	14 (1)	10 (1)	0	1	1	0
Total	14,360 (100)	62 (100)	1,840 (100)	850	774	13†	6†	6†

* Number of infections of this type/number of ICU admissions.
† Average among units.
Acq. = acquired; Card surg = cardiac surgery; Comm = community; Med/surg = medical/surgical.

TABLE II Sites of Infection and Pathogens Isolated

Isolate	Sites				
	GU (n = 120)	Resp (n = 70)	Blood (n = 8)	Other (n = 38)*	Totals (n= 236)*
S. aureus	4	10	3	8	25
E. coli	55	3	2	2	62
KES	14	9	0	3	26
Pseudomonas	7	5	1	1	14
Proteus	8	2	0	3	13
Haemophilus	0	9	0	1	10
Enterococcus	14	0	1	0	15
Candida	7	3	0	3	13
Other†	11	29	1	17	58

* Other sites include wounds, skin and intraabdominal infections.
† Numerous other organisms, no single species representing more than 5% of total.
GU = genitourinary; KES = klebsiella-enterobacter-serratia; Resp = respiratory.

admissions was obtained from a logbook maintained in the CCU and was used to determine the denominator data for infection rates.

Information for each infection episode was entered into a computer file for statistical analysis. Because the objective of the study was to analyze data that were nominally scaled, chi-square methods for contingency tables were used. Tables in the study that displayed statistically significant variations were further analyzed using Tukey-Freeman standardized residuals. These residuals were used to locate differences among infections displaying a particular characteristic. The computations were performed using a BMDP statistical computer package.[12] Because the only statistical test used was the chi-square test of homogeneity of proportions, only p values are reported.

Results

During the 3-year study period there was a total of 5,017 CCU admissions. The annual mortality rate among all patients admitted to the CCU during this study period ranged from 8 to 12%. Two hundred thirty-six infections were documented among 200 patients. Table I lists basic characteristics and rates of infection of the CCU compared with other units within the hospital. Infection rates within the CCU were 5 and 2% for total and CCU-acquired infections, respectively. Compared with other intensive care areas, the CCU accounted for 13% of total infections and 11% of those acquired in intensive care units. One hundred thirty-one (56%) total infections were community-acquired and 90 (38%) were acquired within the CCU. Only 15 (6%) were nosocomially acquired but outside of the CCU.

Table II lists organisms found by sites of infection. Infections of the urinary and lower respiratory tracts were most frequently seen and accounted for 51 and 30% of infections, respectively. *E. coli* was the single most frequently encountered pathogen, accounting for 26% of isolates. *S. aureus* and klebsiella-enterobacter-serratia group each accounted for about 11% of isolates. Cultures were not obtained in 6% of the patients, and in about another 6% of the documented infections no pathogens were isolated.

The mortality rate of patients with infections within the CCU was 22%, an additional 9% died after leaving the CCU. Table III lists patient outcome status compared with both acquisition status and site of infection. For those few patients with more than 1 infection, grouping was tabulated by first infection. Acquisition status had little influence on patient outcome. In all groups, more than 60% of infected patients survived to hospital discharge. However, site of infection was statistically correlated with CCU mortality ($p < 0.001$). Patients with both lower respiratory infections and primary bacteremias were more likely to die in the CCU than those with genitourinary infections ($p < 0.001$).

Discussion

The purpose of this observational study was to explore the epidemiology and importance of infections in CCU patients. Only 1 previous investigation has addressed this issue. Wenzel et al,[1] in a statewide surveillance of nosocomial infections, noted a nosocomial infection rate of 1 to 2% among 13 CCUs that were sur-

TABLE III Patient Outcome Related to Infection Acquisition Status and Site

	Outcome Status			
Acquisition Status	Lived (%)	Died after CCU	Died in CCU	Total
Community	87 (74)	6 (5)	25 (21)	118
CCU-acq.	43 (63)	7 (10)	18 (27)	14
Other nosocomial	9 (64)	4 (29)	1 (7)	68
Total	139 (70)	17 (9)	44 (22)	200
		p = 0.02*		
Site				
Resp	34 (54)	10 (16)	19 (30)	63
GU	87 (82)	6 (6)	13 (12)	106
1° blood	3 (38)	0 (0)	5 (63)	8
Other	15 (65)	1 (4)	7 (30)	22
Total	139 (70)	17 (9)	44 (22)	200
		p <0.001†		

* Difference in distibution of CCU survival among specific acquisition status groups.
† Patients with respiratory or primary bloodstream infections had significantly higher mortality than those with GU infections.
CCU = coronary care unit; other abbreviations as in Table 1 and II.

veyed. However, neither outcome nor acquisition status was addressed, and organisms associated with infections were not studied. A previous study from our institution showed that admission to the CCU comprises approximately 35% of those admitted to all critical care units, but the infections within the CCU comprise only 13% of total infections and 11% of those that are CCU-acquired.[13] That investigation did not specifically address infection-related issues within the CCU itself.

In the present study an overall infection rate of 5% was found. The rate for CCU-acquired infections was about 2%—a rate almost identical to that of the other investigation addressing this issue. However, we could not determine severity of illness or relation of infections to procedures. Our data document that more than 60% of all CCU infections are community-acquired and that 2 to 3% of all patients admitted to the CCU will harbor such infections. Thus, patients admitted to CCU must be evaluated for infection at the time of admission. Almost all of infections originated in either the respiratory or genitourinary tract, and the organisms implicated were those most commonly encountered.

The 22% mortality rate of infected patients while still in the CCU was 2 to 3 times higher than that noted for all CCU patients during the same period. This finding strongly implies that the presence of infection adversely affects patient outcome. The CCU appears to be a less important source of both total and intensive care unit-acquired infection than other critical care areas. However, such infections still occur in almost 5% of patients. An appreciation of these facts may allow better and more rapid assessment of infections, with the potential for decreased morbidity and mortality rates.

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CME Test #28

Effect of Intracoronary Thrombolytic Therapy on Exercise-Induced Ischemia After Acute Myocardial Infarction*

The University of Alabama School of Medicine designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association. Answers are to be marked on the instruction sheet on page A113.

1. In patients receiving streptokinase (SK), baseline angiography revealed that the infarct-related coronary artery was completely obstructed in:
   a) 70%
   b) 95%
   c) 75%
   d) 85%

2. In all patients in this study, past intervention angiography showed patency of the infarct-related coronary artery in:
   a) 50%
   b) 86%
   c) 67%
   d) 54%

3. In comparing patients with incomplete and complete coronary obstruction, peak creatine kinase values were:
   a) lower in patients with incomplete obstruction
   b) lower in patients with complete obstruction recanalized
   c) not significantly different
   d) lower in patients with complete obstruction not recanalized

4. The group that had the longest time for creatine kinase value to peak was:
   a) patients with incomplete obstruction
   b) patients with complete obstruction recanalized
   c) patients with complete obstruction not recanalized
   d) a and b above

5. Thallium-201 defect scores at rest were:
   a) increased in the SK group
   b) increased in the control group
   c) increased in both groups
   d) decreased in both groups

6. The exercise-induced thallium-201 defect score was:
   a) lower in patients with opened vessels
   b) higher in patients with closed vessels
   c) independent of the number of diseased coronary vessels in both groups
   d) none of the above

7. Among patients with 1-vessel disease, ejection fraction increase during exercise was:
   a) higher in closed infarct-related arteries
   b) lower in closed infarct-related arteries
   c) not significantly different among the groups
   d) greater than in patients with 2-vessel disease

8. Patients with acute myocardial infarction treated with SK had improvement in perfusion scintigrams in:
   a) 5 or 6 days
   b) 5 or 6 weeks
   c) 3 or 4 weeks
   d) 3 or 4 months

9. Of the patients undergoing follow-up angiography after thrombolysis, reocclusion has been reported to be:
   a) 8 to 26%
   b) 27 to 54%
   c) 45 to 63%
   d) less than 10 to 32%

10. The optimal management course after successful thrombolytic therapy has:
    a) implications for continued SK use
    b) been possible with nitroglycerin patches
    c) not been defined
    d) none of the above

***This article appears on page 705 of this issue.**

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Determination of Left Ventricular Mass Using Single-Photon Emission Computed Tomography

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To test the hypothesis that single-photon emission computed tomography (SPECT) could actually determine left ventricular LV mass in humans, SPECT measurements of LV mass were compared with LV mass determined by cineangiography in 12 patients with normal coronary arteries and LV function. Repeat SPECT determinations of LV mass were carried out in 5 patients. Projection images of the left ventricle were acquired after intravenous injection of thallium-201 (Tl-201) using a rotating gamma camera. Transverse sections were reconstructed by filtered backprojection. The boundary of LV uptake of Tl-201 in each transverse section was defined using a 3-dimensional threshold detector. Scintigraphic LV mass (total number of voxels demonstrating LV Tl-201 uptake × voxel volume × specific gravity of myocardium) was compared with angiographic LV mass. There was good correlation between LV mass determined by SPECT and that determined by cineangiography. Mean angiographic LV mass was 208 ± 45 g (± standard deviation). Mean SPECT LV mass was 204 ± 42 g. Linear regression analysis revealed the following relation: SPECT LV mass = 0.76 × angiographic LV mass + 46.1 (r = 0.82, root-mean-square deviation from regression = 24.7). The SPECT values of LV mass varied an average of 10.4 ± 4.6% (± standard deviation) in the 5 patients in whom 2 determinations were made. Thus, SPECT of Tl-201 can accurately measure LV mass in humans.

(Am J Cardiol 1985;56:761–764)

The measurement of viable left ventricular (LV) mass may have important prognostic significance in patients with coronary artery disease and cardiac hypertrophy.[1–5] Rackley et al[6] and Kennedy et al,[7] showed that LV mass can be assessed accurately by LV angiography. Recently, several investigators demonstrated that 2-dimensional (2-D) echocardiography is a useful noninvasive means of determining LV mass in selected patients.[8,9] However, this technique makes certain geometric assumptions and is dependent on the quality of the 2-D echocardiogram. Furthermore, this technique does not readily distinguish between viable and nonviable myocardium. Single-photon emission computed tomography (SPECT) is useful as a means of determining viable LV mass in the canine model.[10–11] In this study we tested the hypothesis that SPECT with thallium-201 (Tl-201) may be used to determine LV mass in humans.

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Methods

Patients: We compared SPECT and angiographic measurements of LV mass in 12 consecutive patients who were found to have normal coronary arteries and LV function while undergoing diagnostic left ventriculography and coronary angiography for evaluation of chest pain. Six patients had a history of systemic arterial hypertension and 3 had electrocardiographic evidence of LV hypertrophy. No patient had electrocardiographic criteria for right ventricular hypertrophy.

Angiographic technique: Biplane left ventriculography was accomplished by injecting 56 ml of iodinated contrast material (Renografin-76®, Squibb) over 4 seconds through a pigtail catheter located within the mid-left ventricle. The ventriculogram was recorded simultaneously from the 30° right anterior oblique and 60° left anterior oblique projections on 35-mm Kodak® film at 60 frames/s. Coronary angiography was performed after left ventriculography.

Radionuclide technique: All patients were studied at rest and in the fasting state. Each patient was injected with 2.0 to 2.4 mCi of Tl-201 (New England Nuclear) while standing upright, and allowed to ambulate for 5 minutes. Imaging was begun 10 minutes after Tl-201 injection. Thirty-two images containing a minimum of 80,000 counts were acquired over 180° from the 60° right anterior oblique to the 30° left posterior oblique position using a rotation gamma camera (GE 400T, General Electric Medical Products Division). This camera was equipped with a low-energy (200 keV), general-purpose, parallel-hole collimator and interfaced with a dedicated computer (Medical Data Systems). Planar resolution was 15.7 mm full width half maximum at 20 cm using water as the scatter medium. Each image was acquired at a ditigal resolution of 64 × 64. Total acquisition time was about 30 minutes per study. The projection images were corrected for field nonuniformity using a 90-million-count liquid technetium-99m flood[12] and prefiltered using a 5 × 5 center-weighted spatial filter with a frequency cut-off of 0.15. After correcting for center of rotation, transverse sections (Fig. 1), 1 pixel (0.476 cm) thick, were reconstructed by filtered backprojection. Sections displaying LV uptake of Tl-201 were selected by visual inspection. The epicardial and endocardial boundaries of Tl-201 uptake within these transverse sections were defined by applying a simple 3-dimensional threshold detector to the reconstructed images (Fig. 2). This threshold was 50% of the maximal pixel count within the entire ventricle. The threshold was selected by retrospective analysis of the first 2 studies. In each study, the threshold was adjusted until the scintigraphic LV mass equaled the angiographic LV mass.

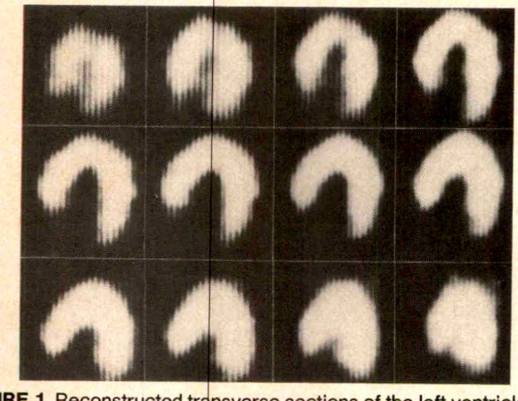

FIGURE 1. Reconstructed transverse sections of the left ventricle from apex (**top left**) to base (**bottom right**).

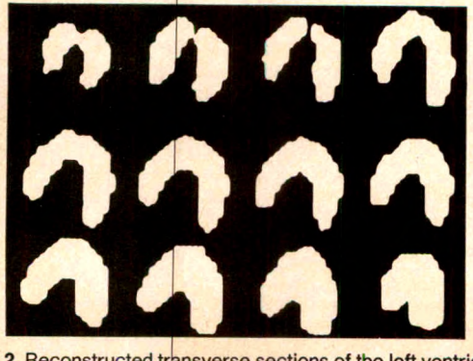

FIGURE 2. Reconstructed transverse sections of the left ventricle after the epicardial and endocardial borders were defined by an automatic 3-dimensional threshold detector. Left ventricular mass was measured from these images.

These 2 empirically derived thresholds were averaged, and this mean threshold value (50% of maximal pixel value/reconstructed volume) was applied prospectively to all studies in a blinded fashion.

In 5 patients, 2 SPECT studies were performed. All SPECT studies were done within 10 weeks of angiography.

Scintigraphic left ventricular mass determination: LV mass was calculated as the total number of volume elements (voxels) demonstrating LV Tl-201 uptake in all sections multiplied by the volume of a single voxel (0.1134 cm^3) and the specific gravity of myocardium (1.05 g/cm^3). Scintigraphic determinations of LV mass were made without knowledge of the value of LV mass calculated by LV angiography. Voxel dimensions were measured using a calibration phantom. All studies were analyzed by 2 independent observers on multiple occasions who were blinded to the results of angiographic determinations of LV mass.

Angiographic left ventricular mass determination: Angiographic determinations of LV mass were made from multiple (3 to 5) end-diastolic frames of a biplane left ventriculogram and averaged. Correction for pin-cushion distortion and calculation of the magnification factor were accomplished using a 3-dimensional coordinate system within the x-ray field as described by Lipscomb.[13] After end-diastolic frames were identified by visual inspection, the endocardial borders were manually traced and digitized on the face of the projector. The thickness of the LV free wall was measured two-thirds of the distance between base and apex. LV mass was then calculated from the following formula, described by Rackley et al[6,7]:

$$\text{LV mass} = \left[4/3\pi\left(\left[\frac{da}{2}+h\right]\times\left[\frac{dl}{2}+h\right]\times\left[\frac{L}{2}h\right]\right)-V\right]1.050$$

where da = transverse diameter from anterior projection, dl = transverse diameter from lateral projection, L = maximal chamber length, and V = volume of the left ventricular chamber.

Statistical methods: The correlation between scintigraphic and angiographic LV mass was obtained with a least squares fit using linear regression analysis.[14] Pearson's r values, calculated from regression analysis, are reported. All mean values are expressed as ± standard deviation. Intra- and interobserver variability are reported as percent variability.

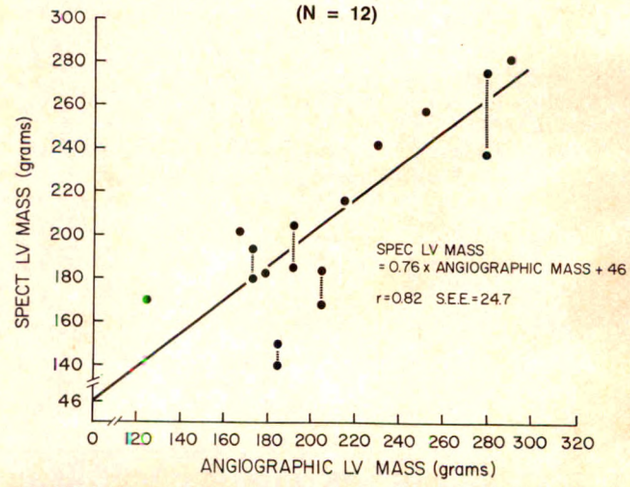

FIGURE 3. Correlation between angiographic and scintigraphic determinations of left ventricular mass. **Vertical dotted lines** connect values of left ventricular (LV) mass measured in 5 patients who had 2 single-photon emission computed tomography (SPECT) studies. S.E.E. = standard error of the estimate.

Results

The correlation between SPECT measurements of LV mass and LV mass determined by cineangiography are shown in Figure 3. Catheterization values of LV mass ranged from 125 to 290 g (mean 208 ± 45 [± standard deviation]). SPECT values of LV mass ranged from 140 to 282 g (mean 204 ± 42). Linear regression analysis revealed the following relation: SPECT LV mass = 0.76 × cath LV mass + 46 (r = 0.82, standard error of the estimate = 24.7 g). SPECT values of LV mass varied an average of 10.4% ± 4.6 in the 5 patients who had 2 SPECT studies. SPECT measurements were reproducible with intraobserver variability of 6% and interobserver variability of 9%. Angiographic determinations of LV mass were reproducible with intra- and interobserver variability of 5%.

Discussion

We[10] and others[11] have shown that SPECT with Tl-201 can accurately quantitate LV mass in the canine model. The present study demonstrates the usefulness of this technique in measuring LV mass in patients. LV mass was calculated from the volume of Tl-201 distribution within the ventricle on reconstructed transverse sections. SPECT LV mass corresponded closely with LV mass determined by ventricular angiography with a Pearson's r value of 0.82 and a standard error of the estimate of 24.7 g.

The fact that SPECT imaging provided good quantitation of LV mass in patients is encouraging when the limitations of this technique are considered. Specifically, image acquisitions were ungated on a system with limited spatial resolution. No correction for attenuation was made. This resulted in blurring of cardiac borders and may account for some overestimation of LV mass. Technical improvements may result in greater resolution and accuracy.

This technique is one of several noninvasive methods that have been used to measure LV mass. Reichek et al[9] reported that 2-D echocardiography, using multiple short-axis images, provides excellent determinations of LV mass. However, this technique is limited by the quality of the images obtainable in a given patient. We obtained 2-D echocardiographic studies in several of the patients described here, but we also found that LV mass was difficult to quantitate in those with chronic obstructive lung disease (COPD) owing to inability to visualize adequately the lateral wall on the short-axis images. In 2 patients with COPD in whom 2-D echocardiographic studies were technically unsatisfactory for quantitation because of lung hyperinflation, 2 of our highest quality SPECT Tl-201 studies were recorded. Pulmonary hyperinflation in patients with COPD may lead to reduced lung attenuation of Tl-201 and result in higher quality SPECT studies. Thus, these techniques may prove complementary in this regard. Peak et al[15] and Iwasaki et al[16] showed that computed tomography can accurately measure LV mass in dogs. Lanzer et al[17] demonstrated that magnetic resonance imaging can accurately quantitate LV mass in vitro in human hearts. All of these techniques have the advantage of better resolution than SPECT. However, further work is necessary to validate these techniques in vivo in humans. The major advantage of SPECT Tl-201 imaging is that it accurately measures perfused LV mass and can differentiate viable from infarcted or ischemic myocardium.

SPECT imaging with Tl-201 to determine LV mass may have important clinical application in patients with ischemic heart disease or marked ventricular hypertrophy. In patients with acute myocardial infarction, the amount of surviving viable myocardium is a major determinant of LV function and prognosis. Because Tl-201 SPECT measures perfused tissue mass, it is ideally suited for assessing the amount of viable LV mass in patients who have had myocardial infarction, and may have an advantage over 2-D echocardiography and computed transmission tomography in this regard. Quantitation of LV mass in patients with cardiac hypertrophy may have important clinical applications as well. In the spontaneously hypertensive rat model, Mirsky et al[18] showed that LV function declines above a certain "critical" LV mass. Linzbach[1,2] suggested that in patients with ventricular hypertrophy, there may be a "critical myocardial weight" above which hypertrophied heart tissue outstrips its blood supply, resulting in a decline in LV function. Furthermore, Gunther and Grossman[19] and Spann et al[20] demonstrated that patients with aortic stenosis who had depressed systolic LV function had significantly more LV hypertrophy than those who presented with normal LV function. Thus, perfused LV mass (or LV mass index) may be a useful prognostic marker in patients with pressure-overload LV hypertrophy and might be useful in the timing of surgical intervention in patients with aortic stenosis.

In conclusion, SPECT of Tl-201 accurately measures LV mass in humans. This technique may find clinical application in patients with coronary artery disease and cardiac hypertrophy.

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Analysis of Factors Affecting the Variability of Fick Versus Indicator Dilution Measurements of Cardiac Output

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This study was performed to assess the relation between Fick and indicator dilution measurements of cardiac output (CO) in a large number of subjects and to evaluate this relation in patients with a low CO, a high CO, and left-sided cardiac regurgitation. In 808 patients (428 men, 380 women, mean age 50 ± 11), CO was measured by Fick and either thermodilution (right atrium to pulmonary artery)(n = 252) or indocyanine green dye ("dye")(pulmonary artery to systemic artery)(n = 556) within 10 minutes of each other. There was excellent agreement between Fick and both thermodilution and dye. The difference between Fick and indicator dilution measurements was 9 ± 9%; it was 10% or less in 67% and 20% or less in 91% of patients. The disparity between Fick and indicator dilution measurements was increased in patients with a low CO (less than 2 liters/min/m^2)(n = 152) (difference 14 ± 11%, p <0.001) and those with aortic or mitral regurgitation (n = 83) (difference 13 ± 11%, p <0.001). In these groups, the disparity between Fick and thermodilution measurements was not exaggerated, but the disparity between Fick and dye measurements was greater. Thus, although there is excellent agreement between Fick and both thermodilution and dye measurements of CO, thermodilution is preferable to dye in patients with a low CO and those with aortic or mitral regurgitation.

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Although several studies have reported good agreement between the Fick and indocyanine green dye ("dye") methods of measuring cardiac output (CO) in humans,[1–3] none has compared the results of Fick and thermodilution in a large number of patients. It is widely believed that the Fick method is more accurate than indicator dilution in patients with a low CO and, in turn, that the indicator dilution technique is more accurate than Fick in those with a high CO,[4] but no previous report has shown an exaggerated disparity between the Fick and indicator dilution techniques in these persons. Finally, there is disagreement as to whether left-sided regurgitation renders the dye method inaccurate. In these patients with left-sided regurgitation, the first-pass dye curve may be prolonged and, as a result, recirculation begins before the downslope of the primary curve is inscribed.[5] The accuracy of thermodilution in those with left-sided regurgitation has not been assessed. Therefore, the present study was performed to address 2 questions: What is the accuracy of the thermodilution and dye techniques compared with Fick in a very large number of patients? Are the accepted differences between Fick and indicator dilution (thermodilution and dye) exaggerated in patients with a low CO, a high CO, and left-sided regurgitation?

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Methods

Patients: From July 1980 to February 1985, CO was measured by both Fick and indicator dilution methods in 808 patients (428 men, 380 women, mean age 50 ± 11 years [± standard deviation], range 18 to 82) referred for cardiac catheterization at Parkland Memorial Hospital, Dallas. All patients gave informed consent. Patients with intracardiac shunting were excluded. Subsequent hemodynamic and cineangiographic evaluation revealed no demonstrable cardiac disease in 146 patients, atherosclerotic coronary artery disease in 399, cardiomyopathy in 68, mitral stenosis in 48, aortic stenosis in 34, primary pulmonary hypertension in 23, constrictive pericarditis in 4, aortic aneurysm in 2, and coarctation of the aorta in 1 patient. Eighty-three patients had cardiac regurgitation: 42 aortic (AR) and 41 mitral (MR); in all cases the regurgitant fraction was more than 0.40 and angiographic grade of regurgitation was 2+, 3+, or 4+.[6]

Measurements of cardiac output: In each patient, catheters were placed in the pulmonary artery and a systemic artery, and CO was measured by the Fick principle. A 3-minute sample of the patient's expired air was collected in a Douglas bag. The patient's nose was firmly clipped shut so that no air could escape through it, after which he or she was asked to hold a special mouthpiece between the lips and to breathe entirely through it. The mouthpiece was attached to the Douglas bag through a 2-way valve with its sidearm open to room air, so that the patient inspired air from the room and expired only into the Douglas bag. Immediately after collection, the contents of the Douglas bag were analyzed by measuring the oxygen content of room air and that of an aliquot of the patient's expired air (with a Beckman oxygen analyzer) and the volume of air in the Douglas bag (with a Tissot spirometer). The oxygen consumption was expressed in milliliters per minute.

The systemic arterial and mixed venous blood samples were drawn into 3-ml heparinized glass syringes, capped, placed on ice, and analyzed immediately with a reflectance oximeter (American Optical). At the same time, a sample of blood was obtained for measurement of hemoglobin concentration. The arteriovenous oxygen difference was calculated as: difference between systemic arterial and mixed venous oxygen saturations × hemoglobin [in g/dl] × 1.39 [ml O_2/g Hgb] × 10 dl/liters. It was expressed as milliliters per liter.

Immediately after Fick determination of CO, CO was measured by thermodilution in 252 patients and by dye in the other 556, according to methods previously described.[7–10] In each patient 3 to 5 measurements were performed and their values averaged. The variability of thermodilution and dye CO values in our laboratory is ±4%. Thus, in all patients, CO was measured in close temporal proximity (within 10 minutes) by Fick as well as by thermodilution (n = 252) or dye (n = 556).

Statistical analyses: In each patient, the CO value by Fick and indicator dilution was divided by the body surface area, yielding the cardiac index. The difference between Fick and indicator dilution CO values was divided by the Fick CO to give the percent difference. Using a Student *t* test,[11] the percent differences in the 252 patients in whom Fick and thermodilution measurements were accomplished were compared with those in the 556 in whom Fick and dye measurements were made. The percentage of patients in whom the Fick and thermal measurements were within 10% and 20% of each other was compared to the percentage in whom Fick and dye measurements were within 10% and 20% of each other using a chi-square analysis.[11,12] These same statistical methods were used to examine the patients in whom the Fick CO was less than 2 liters/min/m^2 (n = 152) or 4 liters/min/m^2 or more (n = 32) as well as those with MR or AR (n = 83). Finally, in both the thermodilution and dye groups, the Fick and indicator dilution cardiac indexes were compared with a 2-variable linear regression analysis.

All data are reported as mean ± standard deviation. For all analyses, a p value <0.05 was considered significant.

Results

For the 808 patients, the Fick COs averaged 2.59 ± 0.68 liters/min/m^2 (range 0.91 to 5.31) and the indicator dilution COs averaged 2.56 ± 0.62 liters/min/m^2 (range 0.96 to 5.38). The 252 patients in whom Fick and thermodilution measurements were performed had an average Fick CO of 2.58 ± 0.60 liters/min/m^2 (range 1.07 to 4.48) and an average thermodilution CO of 2.54 ± 0.54 liters/min/m^2 (range 1.23 to 4.25). The 556 patients in whom CO was measured by Fick and dye methods had an average Fick CO of 2.59 ± 0.73 liters/min/m^2 (range 0.91 to 5.31) and an average dye CO of 2.58 ± 0.70 liters/min/m^2 (range 0.96 to 5.38). The average difference between Fick and indicator dilution COs was 0.23 ± 0.20 liters/min/m^2 (range 0 to 1.39), and the average percentage difference was 9 ± 8% (range 0 to 69%).

Agreement between Fick and indicator dilution techniques: For the 252 patients in whom CO was measured by Fick and thermodilution methods, there was excellent agreement between the 2 techniques ($r = 0.89$, $p < 0.001$, SEE = 0.15 liters/min/m^2). The difference between Fick and thermodilution averaged 8 ± 8%. It was 10% or less in 173 patients (69%) and 20% or less in 234 (93%). For the 556 patients in whom CO was measured by Fick and dye, the correlation between the 2 methods was excellent ($r = 0.91$, $p < 0.001$, SEE = 0.20 liters/min/m^2). The difference between Fick and dye methods averaged 9 ± 9% (difference not significant [NS] compared with the 252 patients in whom CO was measured by Fick and thermodilution methods). The percentage difference was 10% or less in 369 patients (66%) and 20% or less in 499 (90%) (NS compared with patients in whom CO was measured by Fick and thermodilution methods).

Influence of a low cardiac output on the Fick-indicator dilution relation: In 152 patients, the Fick CO value was less than 2 liters/min/m^2. In these patients, the difference between Fick and indicator dilution CO averaged 0.22 ± 0.17 liters/min/m^2, and the difference was 14 ± 11%. The difference between Fick and indicator dilution was 10% or less in only 73 patients (48%) and 20% or less in only 117 (77%) (Table I). The Fick CO value exceeded the indicator dilution CO value by more than 0.05 liters/min/m^2 in 103 patients, (68%), whereas the opposite occurred in only 25 (16%) ($p < 0.001$)(Table II).

Of the 624 patients with a Fick CO of 2.00 to 3.99 liters/min/m^2, the absolute difference between Fick and indicator dilution CO was 0.22 ± 0.20 liters/min/m^2 (NS compared with the 152 patients with a CO of less than 2 liters/min/m^2), but the difference was 8 ± 7% ($p < 0.001$ compared with the 152 with a CO of less than 2 liters/min/m^2). In 72% the difference between Fick and indicator dilution was 10% or less and in 94% it was 20% or less, both significantly greater than the values for the

TABLE I Influence of a Low Cardiac Output (CO) on the Fick-Indicator Dilution Relation

	CO <2 liters/min/m²	CO 2.00–3.99 liters/min/m²	χ^2	p
	Fick Versus Thermodilution and Dye (n = 152)	(n = 624)		
Fick-indicator dilution difference ≤10%	73 (48%)	450 (72%)	32.278	<0.001
Fick-indicator dilution difference ≤20%	117 (77%)	589 (94%)	45.180	<0.001
	Fick Versus Thermodilution Only (n = 39)	(n = 207)		
Fick-thermodilution difference ≤10%	25 (64%)	147 (71%)	0.745	0.388
Fick-thermodilution difference ≤20%	31 (79%)	201 (97%)	18.971	<0.001
	Fick Versus Dye Only (n = 113)	(n = 417)		
Fick-dye difference ≤10%	51 (45%)	303 (73%)	30.378	<0.001
Fick-dye difference ≤20%	89 (79%)	388 (93%)	20.157	<0.001

TABLE II Relation of Fick and Indicator Dilution Measurements of Cardiac Output (CO) in Patient Subgroups

Fick CO <2 liters/min/m² (n = 152)	
Fick CO > indicator dilution CO by >0.05 liters/min/m²	103*
Fick and indicator dilution COs within 0.05 liters/min/m²	24
Fick CO < indicator dilution CO by >0.05 liters/min/m²	25
Fick CO ≥4 liters/min/m² (n = 32)	
Fick CO > indicator dilution CO by >0.05 liters/min/m²	7
Fick and indicator dilution COs within 0.05 liters/min/m²	0
Fick CO < indicator dilution CO by >0.05 liters/min/m²	25†
Aortic or Mitral Regurgitation (n = 83)	
Fick CO >indicator dilution CO by >0.05 liters/min/m²	44
Fick and indicator dilution COs within 0.05 liters/min/m²	20
Fick CO < indicator dilution CO by >0.05 liters/min/m²	29

* p <0.001 compared to the other 2 groups with a CO <2 l/min/m²;
† p <0.001 compared to the other 2 groups with a CO ≥4 l/min/m².

152 patients whose Fick COs were less than 2 liters/min/m² (Table I).

The difference between Fick and thermodilution was 10% or less in 25 of the 39 patients (64%) with a Fick CO of less than 2 liters/min/m², whereas the difference between Fick and dye was 10% or less in only 51 of the 113 patients (45%) with a Fick CO of less than 2 liters/min/m² ($\chi^2 = 4.173$, p = 0.041).

Thus, although the absolute difference between Fick and indicator dilution measurements of CO was not altered by a CO of less than 2 liters/min/m², the percentage difference between them was significantly increased when CO was less than 2 liters/min/m². This was true for dye but not for thermodilution measurements.

Influence of a high cardiac output on the Fick-indicator dilution relation: Of the 808 patients, only 32 had a Fick CO 4 liters/min/m² or more; the difference between Fick and indicator dilution in these patients was 9 ± 6%. In 20 (63%) the difference between Fick and indicator dilution was 10% or less, and in 30 (94%) it was 20% or less (Table III). The indicator dilution CO exceeded the Fick CO by more than 0.05 liters/min/m² in 25 patients (78%), whereas the opposite was true in only 7 (22%) (p <0.001) (Table II).

Of the 624 patients with a CO of 2.00 to 3.99 liters/min/m², the difference between Fick and indicator dilution was 8 ± 7% (NS compared with the 32 with a CO of 4 liters/min/m² or more). In 449 patients (72%), the difference between Fick and indicator dilution was 10% or less and in 586 (94%) it was 20% or less (NS compared with those with a CO of 4 liters/min/m² or more). The relation between Fick and both thermodilution and dye was similar (Table III). Thus, the difference between Fick and indicator dilution methods was not influenced substantially by a CO of 4 liters/min/m² or more.

Influence of aortic or mitral regurgitation on the Fick indicator dilution relation: Eighty-three patients had AR or MR of the severity previously described. For these patients, the absolute difference between Fick and indicator dilution CO averaged 0.32 ± 0.28 liters/min/m², and the percent difference was 13 ± 11%. In contrast, 725 patients had mild or no regurgitation; in these patients, the absolute difference between Fick and indicator dilution was 0.21 ± 0.18 liters/min/m² and the percent difference was 9 ± 8% (both p <0.001 in comparison to the 83 with regurgitation). The difference between Fick and indicator dilution was 10% or less in 41 of the 83 patients (49%) with regurgitation and in 501 of the 725 (69%) without it (p <0.001) (Table IV). The difference between Fick and thermodilution was 10% or less in 11 (73%) of the 15 with regurgitation, whereas the difference between Fick and dye was 10% or less in only 30 of the 68 patients (44%) with regurgitation ($\chi^2 = 4.196$, p = 0.041).

The 83 patients with AR or MR had an average Fick CO of 2.43 ± 0.73 liters/min/m² (range 0.91 to 5.16). Of these, 56 had a CO of 2 liters/min/m² or more, whereas the other 27 had a CO of less than 2 liters/min/m². The increased disparity between Fick and dye in the patients with regurgitation was unrelated to a low (less than 2 liters/min/m²) CO.

In short, the absolute and percentage differences between Fick and indicator dilution measurements of

TABLE III Influence of a High Cardiac Output (CO) on the Fick-Indicator Dilution Relation

	CO ≥4 liters/min/m²	CO 2.00–3.99 liters/min/m²	χ^2	p
	Fick Versus Thermodilution and Dye (n = 32)	(n = 624)		
Fick-indicator dilution difference ≤10%	20 (63%)	449 (72%)	1.335	0.248
Fick-indicator dilution difference ≤20%	30 (94%)	586 (94%)	0.001	0.971
	Fick Versus Thermodilution Only (n = 6)	(n = 207)		
Fick-thermodilution difference ≤10%	4 (67%)	144 (70%)	0.023	0.879
Fick-thermodilution difference ≤20%	5 (83%)	198 (96%)	1.978	0.160
	Fick Versus Dye Only (n = 26)	(n = 417)		
Fick-dye difference ≤10%	16 (62%)	302 (72%)	1.431	0.232
Fick-dye difference ≤20%	25 (96%)	385 (92%)	0.520	0.471

TABLE IV Influence of Aortic or Mitral Regurgitation on the Fick-Indicator Dilution Relation

	Regurgitation	No Regurgitation		
	Fick Versus Thermodilution and Dye (n = 83)	(n = 725)	χ^2	p
Fick-indicator dilution difference ≤10%	41 (49%)	501 (69%)	13.096	<0.001
Fick-indicator dilution difference ≤20%	64 (77%)	669 (92%)	20.346	<0.001
	Fick Versus Thermodilution Only (n = 15)	(n = 237)		
Fick-thermodilution difference ≤10%	11 (73%)	163 (69%)	0.137	0.711
Fick-thermodilution difference ≤20%	13 (87%)	221 (93%)	0.922	0.337
	Fick Versus Dye Only (n = 68)	(n = 488)		
Fick-dye difference ≤10%	30 (44%)	338 (69%)	16.861	<0.001
Fick-dye difference ≤20%	51 (75%)	448 (92%)	18.315	<0.001

CO were significantly increased when AR or MR was present. This was true for the dye technique but not for thermodilution.

Discussion

Although numerous techniques have been introduced to measure CO in humans, 2—the Fick principle and the indicator dilution technique—are generally accepted and widely used. Dye has been used extensively, but recently the thermodilution technique has been frequently used in catheterization laboratories and intensive care units. Three reports[1–3] have shown that Fick and dye measurements of CO are within 20 to 25% of each other in 75 to 90% of patients. Our data are in agreement with these reports: Of the 556 patients in whom Fick and dye measurements were performed, the difference between them was 10% or less in 66% and 20% or less in 90% of patients.

Agreement between Fick and thermodilution measurements of cardiac output: Although 3 studies[1–3] compared Fick and dye in hundreds of subjects, the accuracy of the thermodilution method has not been thoroughly assessed. Branthwaite and Bradley[13] showed a good relation between Fick and thermodilution measurements in 17 patients. They injected saline solution of room temperature into the internal jugular vein and measured the change in temperature in the pulmonary artery with a single-thermistor catheter. Ganz et al,[14] using a catheter with 2 thermistors, showed good agreement between thermodilution and dye in 20 patients. Our data, obtained with modern, balloon-tipped thermal catheters in 252 patients, demonstrate excellent agreement between Fick and thermodilution methods ($r = 0.89$, $p < 0.001$; SEE = 0.15 liters/min/m²), and the results of Fick and thermodilution measurements are similar to those of Fick and dye. Thus, compared with Fick, thermodilution and dye are of comparable accuracy.

Influence of a low or high cardiac output on the agreement between Fick and indicator dilution: The Fick method is widely believed to be more accurate than indicator dilution in patients with a low CO and

indicator dilution is believed to be preferable in those with a high CO,[4] but no previous report has shown that the 2 techniques are disparate in these patients. Our data show that the average difference between Fick and indicator dilution is greater in patients with a CO of less than 2 liters/min/m^2 (14 ± 11%, n = 152) compared with those whose COs are 2.00 to 3.99 liters/min/m^2 (8 ± 7%, n = 624, p <0.001). Furthermore, the Fick-indicator dilution difference was 10% or less in only 48% and 20% or less in only 77% of the 152 patients with a CO of less than 2 liters/min/m^2; in contrast, the Fick-indicator dilution difference is 10% or less in 72% and 20% or less in 94% of the 624 patients with a CO of 2.00 to 3.99 liters/min/m^2 (p <0.001)(Table I).

The increased disparity between Fick and indicator dilution in patients with a low CO is true for the dye method but not for thermodilution. In the patient with a low CO, right-sided injection of dye, with sampling from a systemic artery, may produce a first-pass indicator dilution curve that is so prolonged that recirculation begins before the downslope of the primary curve is inscribed. As a result, measurement of CO may be inaccurate. Theoretically this inaccuracy should not occur with thermodilution because it assesses and measures the curve's shape and area after the right-sided injection and sampling of indicator. Our data reveal a difference between thermodilution and dye measurements. Patients with a CO of less than 2 liters/min/m^2 had an increased disparity between Fick and dye, but not between Fick and thermodilution (Table I).

Although Eliasch et al[2] suggested that the difference between Fick and dye values was exaggerated in patients whose COs were more than 9 liters/min, no subsequent study has provided data to support this. In the present study, only 32 patients had a CO of 4 liters/min/m^2 or more. The relation between Fick and indicator dilution in these patients was similar to that in the 624 patients with a CO of 2.00 to 3.99 liters/min/m^2 (Table III). Therefore, our data do not show that the Fick-indicator dilution disparity is influenced by a high CO (4 liters/min/m^2 or more), but the relatively small number of patients with a high CO may have prevented us from assessing this issue definitively.

Influence of aortic or mitral regurgitation on the agreement between Fick and indicator dilution: There is disagreement as to whether left-sided regurgitation renders the indicator dilution technique inaccurate. In patients with severe MR, Rahimtoola and Swan[5] measured CO by injecting dye into the pulmonary artery and sampling its appearance and concentration in a systemic artery; the resultant dye curves underestimated CO by about 20%. These investigators argued that the distortion of the dye curves, with a resultant miscalculation of CO, was caused by recirculation of indicator in the coronary arterial system. Samet et al[15,16] showed that CO could be measured reliably by the right-sided injection and sampling of dye (right atrium to pulmonary artery) even in patients with severe MR or AR. In these patients, the problem imposed by coronary recirculation was alleviated and, as a result, the dye curves were not distorted in shape or area. Our data complement these observations. In those with AR or MR (n = 83), the Fick-indicator dilution percentage difference was exaggerated (13 ± 11%) compared to those without regurgitation (n = 725) (9 ± 8%, p <0.001). However, the disparity between Fick and indicator dilution was present for dye (for which indicator was injected into the pulmonary artery and sampled in a systemic artery), but not for thermodilution (for which indicator was injected into the right atrium and sampled in the pulmonary artery) (Table IV).

Clinical implications: Our data indicate excellent agreement between Fick and both thermodilution and dye measurements of CO. Thermodilution appears to be preferable to dye in patients with a low CO and those with AR or MR. In these patients, the right-sided injection and sampling of "cold" yields a curve less subject to recirculation-induced distortion than the right-sided injection and left-sided sampling of dye.

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INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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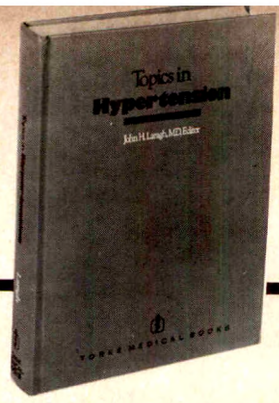

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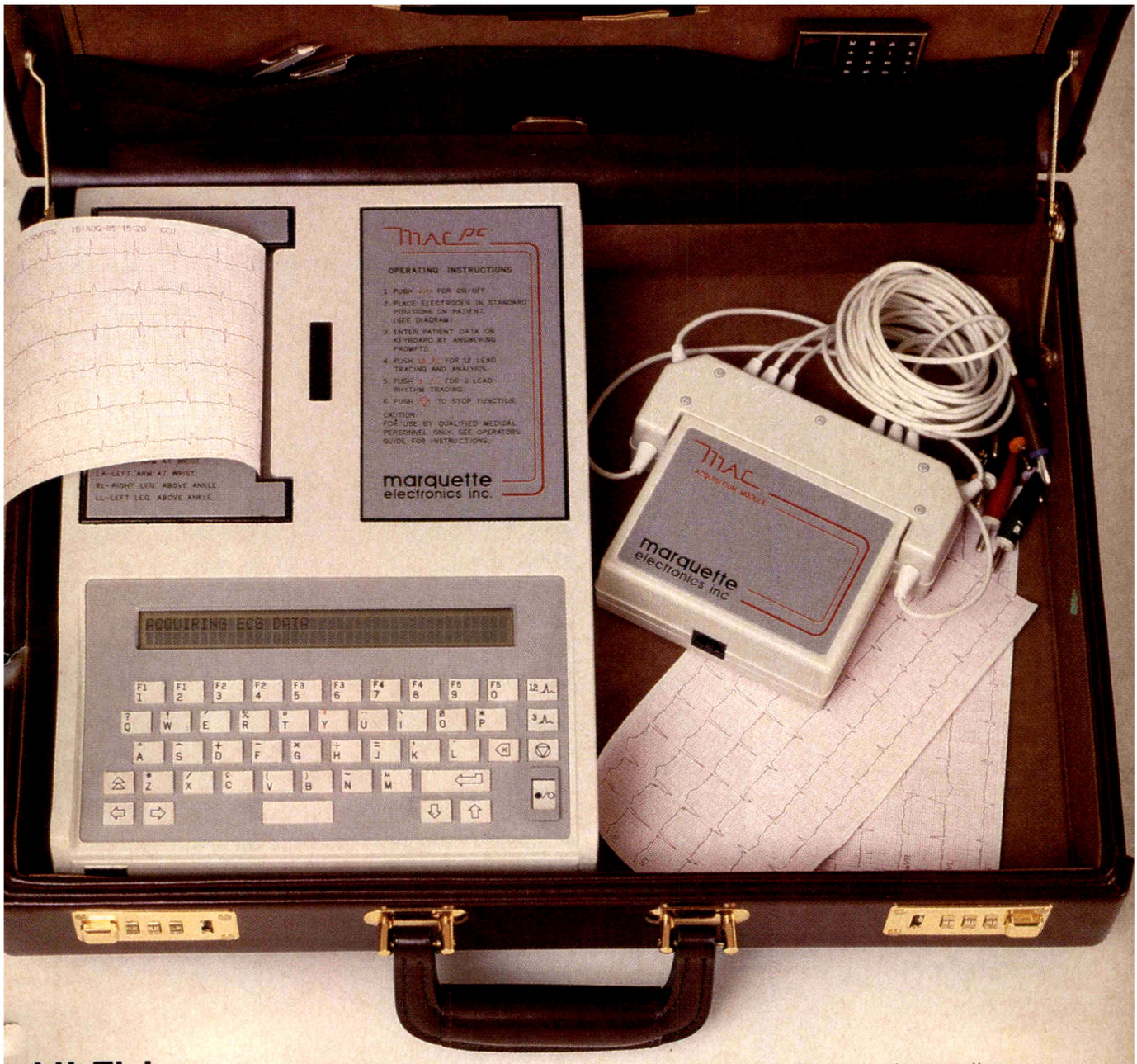

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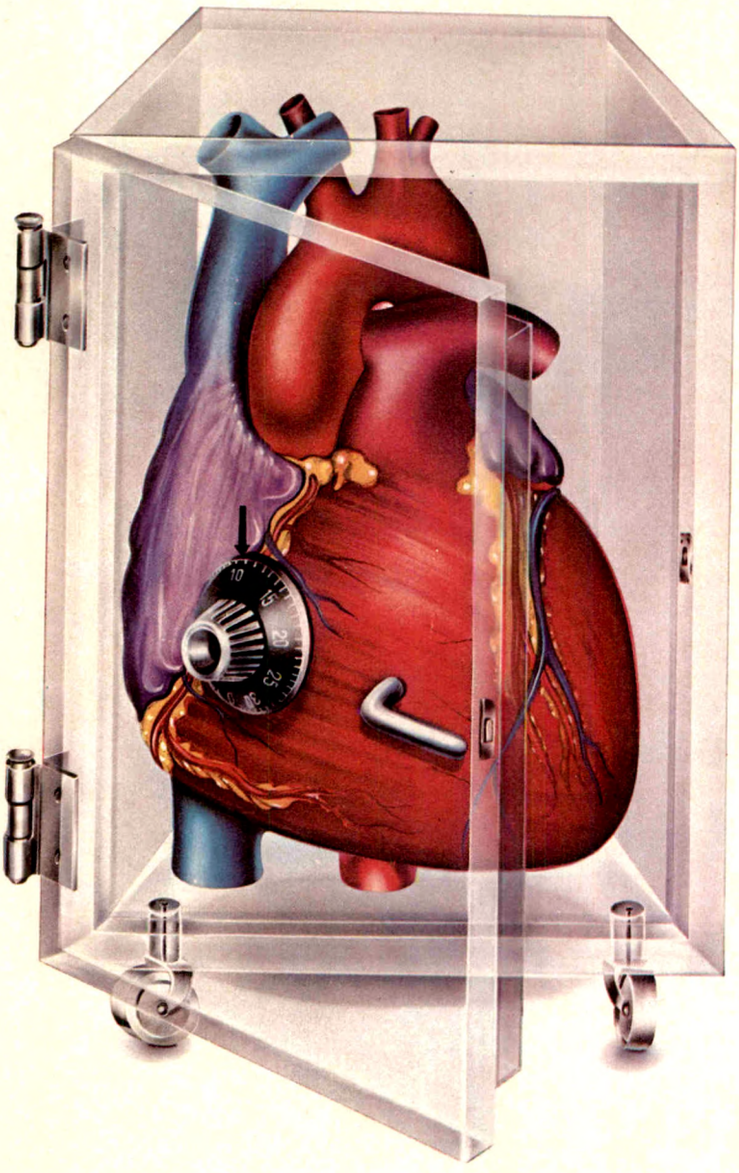
In hypertension...
the risks of some diuretics
or the protection of Lopressor



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*Exerts a relative preference for beta-one receptors; this preference is not absolute.

Contraindicated in heart block greater than first degree, sinus bradycardia, cardiogenic shock, and overt heart failure. Side effects with Lopressor are generally mild and transient, the most common being tiredness, dizziness, depression, and diarrhea.

Please see next page for Brief Summary of Prescribing Information.

Lopressor®

metoprolol tartrate

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Prefilled Syringes: 5 mg/5 ml

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Geigy

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metoprolol tartrate

C84-38 (Rev. 7/85)

Tablets
Ampuls
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BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.
Myocardial Infarction
Lopressor ampuls, prefilled syringes and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Hypertension
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; significant heart block greater than first degree (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice (see **PRECAUTIONS, Information for Patients**).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should know how they react to this medicine before they operate automobiles and machinery or engage in other tasks requiring alertness. Patients should contact the physician if any difficulty in breathing occurs, and before surgery of any type, the patient should inform the physician or dentist that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a 1-year study in dogs, there was no evidence of drug-induced toxicity at or below oral dosages of 105 mg/kg per day. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.
Pregnancy Category B
Reproduction studies have been performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg and have revealed no evidence of impaired fertility or teratogenicity due to Lopressor. Increased postimplantation loss and decreased neonatal survival did occur in the rats (threshold between 50 and 500 mg/kg), and distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported, but a drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; and congestive heart failure have been reported. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) has been reported in fewer than 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100, or fewer, patients.

Hypersensitive Reactions: Pruritus has occurred in fewer than 1 of 100 patients. Rash has been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Alopecia has been reported.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

C84-38 (Rev. 7/85)

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Changing the Course of Cardiovascular Care

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Effect of Damped Sine-Wave Shocks on Catheter Dielectric Strength

GUST H. BARDY, MD, FERNANDO COLTORTI, MD, TOM D. IVEY, MD, DAN YERKOVICH, and H. LEON GREENE, MD

This study evaluated the ability of 24 new standard tripolar and quadripolar U.S. Catheter Instruments catheters to withstand a single damped sinusoidal shock delivered by a standard defibrillator. The schema for energy delivery was meant to simulate possible clinical practices. Delivered peak voltage and current were measured during each shock. Each electrode was examined for pitting and changes in line resistance as a consequence of the shock. Electrode pitting occurred on all selected anodal poles. However, it also was found on "unsolicited" electrodes from 7 catheters, indicating that current had followed unanticipated routes. Electrode line resistance was unmeasurable in 6 of these 7 inappropriately pitted electrodes.

Delivered peak voltage and postshock catheter dielectric strength depended on the manner of energy delivery. To simulate a posterior septal accessory pathway ablation procedure, a shock was delivered to 2 proximal (anodal) poles in 16 quadripolar catheters (8 received 200 J and 8 received 360 J). Delivered peak voltage was 3,125 ± 362 V for the 200-J shock and 4,100 ± 160 V for the 360-J shock. Postshock catheter dielectric strength for the 200- and 360-J shock was 1,425 ± 826 V and 601 ± 707 V, respectively. This was significantly lower than peak delivered voltage ($p < 0.001$ for either energy).

To simulate His bundle or ventricular tachycardia focus ablation, 8 tripolar catheters each received a single 200-J shock to the tip electrode. This resulted in a delivered peak voltage of 2,900 ± 351 V, compared with a postshock dielectric strength of 1,325 ± 1,320 V ($p < 0.002$).

It is concluded that standard catheters cannot control current flow adequately during a single high-energy shock because of inadequate dielectric strength. After the first shock an already inadequate dielectric strength deteriorates and increases the likelihood of current leakage with each subsequent shock.

(Am J Cardiol 1985;56:769–772)

Standard electrode catheters may have significant limitations when subjected to high-energy defibrillator shocks for ablation of cardiac tissue. For example, some catheters can develop open circuits or visible changes in insulation after multiple defibrillator shocks.[1] These observations led us to question the likelihood of developing serious nonvisible defects in commonly used, commercially available catheters during and after a single defibrillator shock. The results have implications for the safety of procedures that deliver high energies to standard catheters for ablation of atrioventricular (AV) nodes, accessory pathways and ventricular tachycardia foci.

From the Divisions of Cardiology and Cardiac Surgery, Harborview Medical Center, University of Washington, Seattle, Washington. This work was supported in part by the American Heart Association, Washington Affiliate, and by the Seattle Emergency Medical Services Foundation, Seattle, Washington. Dr. Coltorti is a recipient of a fellowship grant from the Ministero della Pubblica Istruzione, Italy. Manuscript received March 28, 1985; revised manuscript received May 10, 1985, accepted May 13, 1985.

Address for reprints: Gust H. Bardy, MD, Harborview Medical Center, 325 Ninth Avenue, Seattle, Washington 98104.

Methods

Twenty-four U.S. Catheter Instruments (USCI) standard 6Fr recording and pacing catheters (16 quadripolar and 8 tripolar) with interelectrode spacing of 1.0 cm were studied. Each catheter was new and had never been used for any purpose before testing other than visual inspection and measurement of line resistance.

Each catheter was positioned in the right atrium or coronary sinus of a dog by way of a femoral or jugular vein. A single 200- or 360-J damped sinusoidal discharge was delivered to each catheter by a standard Physio-Control Life-Pak 6 using techniques described previously.[1–11] The catheter was connected to the positive output (anode) of the defibrillator. An 8.5-cm disc positioned on the chest was used as the negative pole (cathode). Anode-cathode configuration differed for the quadripolar and tripolar catheters. For quadripolar catheters, 2 adjacent proximal poles were connected in parallel as the anode, as might be done for accessory pathway ablation through the coronary sinus. For tripolar catheters, the distal pole was used as the anode, as might be done during AV node/His bundle or ventricular tachycardia focus ablation. The energy used for quadripolar catheters was either 200 or 360 J (8 catheters were tested with each energy level). All 8 tripolar catheters received 200-J shocks. Both current and voltage waveforms were monitored during delivery of the shock. Current was measured with a Tektronix A6303 current probe. Voltage was measured differentially using a resistive

voltage divider with a 1000:1 input to output ratio (Warren Heggen, University Scientific Instruments Shop) and was displayed simultaneously with the current on a Tektronix #5113A oscilloscope.

After the shock, each catheter was inspected by microscopy for electrode pitting (i.e., melting of the electrode surface) and line resistance was measured for each pole. Catheter dielectric strength was determined with a variable output potential generator that subjected the electrodes to a gradually increasing voltage (Hipotronics). The voltage at which current leakage occurred through the insulation separating the anodal electrodes from other catheter electrodes was catheter dielectric strength. Dielectric strength could be measured meaningfully only once per catheter, because leakage of current through insulation resulted in progressive deterioration in insulation properties.

Catheter dielectric strength subsequently was correlated with peak shock voltage. Dielectric strength of shocked catheters also was compared with the dielectric strength of 5 new unshocked quadripolar catheters.

Statistical comparisons of peak-delivered voltages and dielectric strength were performed with paired *t* tests.

Results

The data are summarized in Table I. Of the 24 catheters studied, pitting was observed on the electrode receiving the shock in each instance. However, on 7 catheters (4 quadripolar and 3 tripolar), pitting was observed on poles *not* intended to have received a shock. This finding indicates inappropriate current discharge to electrodes not intentionally serving as part of the anode. An example is shown in Figure 1, in which pole 2 of a quadripolar catheter is unexpectedly pitted after a 360-J shock to anodal poles 3 and 4.

Catheter line resistance of the distal electrode for either the quadripolar or tripolar catheters was unaffected by the shock (2.0 ± 0.1 ohms before and 2.0 ± 0.1 ohms after). However, the more proximal poles did develop changes in line resistance after the shock. Before the shock, the more proximal poles had a line resistance of 3.3 ± 0.1 ohms. After the shock, it either was unchanged (3.3 ± 0.1 ohms in 18 catheters) or it was open ("infinite" resistance in 6 catheters).

Delivered peak voltage and current during the 200-J quadripolar catheter shocks were 3,125 ± 362 V and 22 ± 5 A, respectively. In comparison, the mean dielectric strength of these catheters after the 200-J shock was 1,425 ± 826 V. Peak delivered voltage was significantly higher than dielectric strength ($p < 0.001$). For the 360-J quadripolar catheter shocks, peak voltage and current were 4,100 ± 160 V and 30 ± 3 A. Postshock dielectric strength was 601 ± 707 V ($p < 0.001$). For the 200-J tripolar catheter shocks, the peak voltage and current were 2,900 ± 351 V and 31 ± 10 A. The dielectric strength for the 200-J shocks to the tripolar catheter was 1,325 ± 1,320 V ($p < 0.002$).

The 5 new quadripolar catheters not subjected to defibrillator shocks had dielectric strengths between

TABLE I Data on 24 Catheters

Catheter Size	Anode Poles	Stored Energy (J)	Pitting on Non-Anode Poles	Change in Electrode Resistance	Peak Delivered Current (A)	Peak Delivered Voltage (V)	Dielectric Strength (V)
Effects of a 200-J Shock to Two Proximal Poles of a Quadripolar Catheter							
6Fr	3 + 4	200	0	0	19	3,300	200
6Fr	3 + 4	200	0	0	18	3,400	1,900
6Fr	3 + 4	200	0	0	15	3,400	2,500
6Fr	3 + 4	200	0	0	19	3,200	300
6Fr	2 + 3	200	0	0	28	2,600	1,500
6Fr	2 + 3	200	0	0	30	2,500	1,500
6Fr	3 + 4	200	0	0	23	3,300	2,200
6Fr	3 + 4	200	0	0	23	3,300	1,300
					22 ± 5	3,125 ± 362	1,425 ± 826
						($p < 0.001$)	
Effects of a 360-J Shock to Two Proximal Poles of a Quadripolar Catheter							
6Fr	3 + 4	360	0	0	29	4,000	800
6Fr	3 + 4	360	+(2)*	+ (open)	32	4,000	70
6Fr	3 + 4	360	+(2)	+ (open)	32	4,000	70
6Fr	3 + 4	360	0	0	29	4,100	500
6Fr	3 + 4	360	0	0	26	4,200	2,200
6Fr	2 + 3	360	+(4)	+ (open)	29	4,400	70
6Fr	3 + 4	360	+(2)	0	35	3,900	400
6Fr	2 + 3	360	0	0	26	4,200	70
					30 ± 3	4,100 ± 160	601 ± 707
						($p < 0.001$)	
Effects of a 200-J Shock to the Distal Pole of a Tripolar Catheter							
6Fr	1	200	+(3)*	+ (open)	23	3,200	800
6Fr	1	200	0	0	23	3,100	3,000
6Fr	1	200	+(2,3)	+ (open)	24	3,200	1,000
6Fr	1	200	0	0	25	3,200	1,800
6Fr	1	200	0	0	25	3,000	300
6Fr	1	200	0	0	47	2,300	3,500
6Fr	1	200	+(3)	+ (open)	40	2,600	100
6Fr	1	200	0	0	38	2,600	100
					31 ± 10	2,900 ± 351	1,325 ± 1,320
						($p < 0.002$)	

* Numbers in parentheses refer to pole pitted.

2,200 and 3,500 V (2,780 ± 517). In contrast, dielectric strength of shocked catheters generally was much lower (see before) and varied between 70 and 3,500 V (Table I). The difference in dielectric strength between shocked and unshocked quadripolar catheters was significant at the $p < 0.001$ level.

Discussion

Previous work assessing integrity of standard pacing and recording catheters subjected to defibrillator shocks was done after multiple discharges.[1] The study included visual inspection of catheters and measurement of line resistance of each electrode before and after shocking. Several catheter brands were incapable of sustaining multiple high-energy shocks either by demonstrating increases in line resistance or by showing gross visible deterioration in the insulation. Our work expands on these observations by evaluating both catheter structure and dielectric strength during and after a single damped sinusoidal shock.

None of our catheters that received single shocks had visible defects in insulation and only 6 had changes in line resistance. Each of these 6 catheters also demonstrated inappropriate electrode pitting and deterioration of dielectric strength (1,000 V or less in these 6 catheters). The open circuits indicate marked changes in catheter structure that likely correspond to fusion of the weld between ring electrode and cable.

In 18 catheters line resistance was unchanged. However, this finding alone did not predict whether a catheter's insulation was sufficient to prevent current leaks during defibrillation shocks. Thirteen of these 18 catheters had a dielectric strength less than 2,200 V after the shock—levels inadequate to prevent current leakage for subsequent high-energy shocks. Intact line resistance, therefore, does not guarantee that the catheter insulation is unchanged.

New USCI, unshocked quadripolar catheters in our study had dielectric strength between 2,200 and 3,500 V. The delivered peak voltage during a shock to quadripolar catheters using a 200-J discharge ranged between 2,500 and 3,200 V. For a 360-J discharge it was between 3,900 and 4,200 V. Clearly, the possibility to exceed a catheter's maximally tolerated voltage is present during the first shock. For all the catheters studied, the dielectric strength after 1 shock was less than 2,200 V in 19 of 24 (79%) instances and was less than 1,000 V in 13 (54%). This implies an even greater likelihood of misdirected shocks for catheters used more than once. The deterioration in catheter dielectric strength to a value far less than originally present probably results from structural changes in the insulation during the initial shock.

Inappropriate current discharge was documented during the first shock in 7 catheters. In these catheters, unconnected nonanodal electrodes demonstrated pitting (platinum melting) on their surfaces, indicating that part of the current exited elsewhere than originally intended (Fig. 1). In the case of AV node/His bundle ablation, such current leakage probably will not cause any unwanted cardiac damage. The distal electrode is usually used in these instances, and therefore, an inappropriate current discharge through a more proximal electrode is unlikely to affect vital tissue, because the current leak will probably enter the atrial cavity and be dissipated in the blood. Such an occurrence, however, will result in a diminution in current at the tip electrode and therefore may not be adequate to damage the AV node/His bundle to create heart block. This may account for failure of the technique in some instances, especially with newer model USCI catheters.[1]

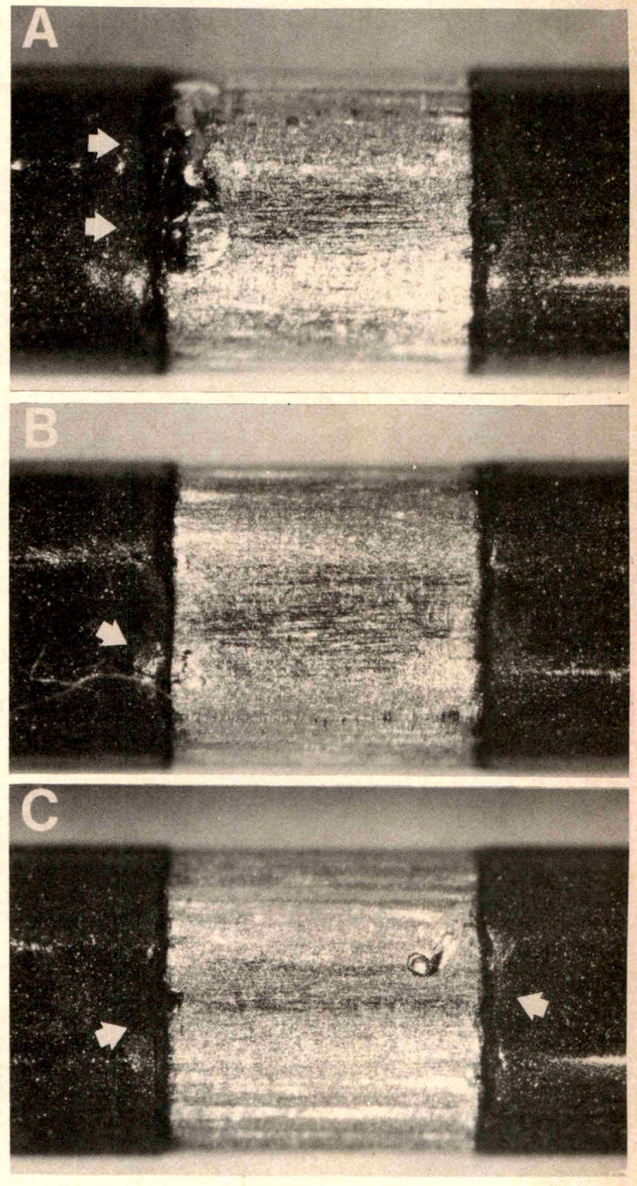

FIGURE 1. Electrode pitting (platinum melting) is designated by **white arrows** on 3 of the 4 poles of a standard 6 Fr U.S. Catheter Instruments quadripolar catheter after a single 360-J shock (peak voltage of 4,000 V and peak current of 32 A). Poles 4 and 3 served jointly as the anode (positive electrode), as might be done during at attempted posterior septal accessory pathway ablation. Pitting is seen on pole 4 (**A**) and pole 3 (**B**) as would be expected. Pitting is much more pronounced on pole 4, possibly indicating asymmetric current flow. The unanticipated pitting on pole 2 (**C**) indicates inappropriate electrical discharge through this electrode, which was not intended to serve as a part of the anodal configuration. Line resistance for pole 2 was not measurable (i.e., an open circuit). Dielectric strength after the shock was only 70 V. Pole 1 was intact and is not shown

Misdirected currents in the coronary sinus may have more significant untoward effects. Current leakage during posteroseptal accessory pathway ablation attempts could result in damage to parts of the AV groove away from the intended accessory pathway. This is a particular concern with respect to coronary artery injury. Patients considered for catheter ablation procedures should be those with no significant coronary artery near the accessory pathway. An inappropriate discharge 1 to 2 cm away from the intended delivery site might result in coronary artery injury. Furthermore, as with AV node/His bundle ablation, current leakage may result in failure of the technique to interrupt accessory AV conduction.

The concerns expressed for AV node/His bundle and accessory pathway ablation also exist for shocks delivered to ventricular tachycardia foci. Undesired current discharge might result in failure of the procedure or in damage to normal myocardium not intended to be injured.

Simple means of monitoring quality of catheter insulation for the electrophysiologist are not available. Delivering high-energy defibrillator shocks to standard catheters may result in misdirected currents with the first shock. Furthermore, one must assume that catheter insulation deteriorates after a single 200-J or higher energy shock making multiple shocks to the same catheter ill-advised. Leakage of current to "unsolicited" anodal electrodes may result in failure of the technique or an undesired outcome. Catheter technology must be improved before catheter ablation procedures can be refined or an alternative form of energy delivery will be required.

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Value of Intraoperative Left Ventricular Microbubbles Detected by Transesophageal Two-Dimensional Echocardiography in Predicting Neurologic Outcome After Cardiac Operations

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To determine whether the presence or absence of left ventricular (LV) intracavitary microbubbles during cardiac surgery predicts neurologic sequelae, 82 patients undergoing cardiac surgery were studied using transesophageal 2-dimensional (2-D) echocardiography. Cross-sectional images were recorded just before and immediately after cardiopulmonary bypass and stop frames were reviewed for the presence of microbubbles, rated as: 0 = absent, 1 = fewer than 5/frame, 2 = 10 to 25/frame, 3 = too numerous to count. Microbubbles were detected after cardiopulmonary bypass in 34 patients (41%) and found more often in valvular or other intracardiac manipulations than in coronary revascularization, 30 of 40 vs 4 of 42, respectively ($p < 0.001$). When grade 2 or 3 microbubbles were identified (22 of 34 patients), mechanical attempts to eradicate them were not successful. Postoperative follow-up in all patients revealed no new focal neurologic deficits. Prolonged encephalopathy (confusional state more than 72 hours) occurred in 4 of 48 patients with no detectable microbubbles and in 3 of 34 patients with microbubbles (difference not significant). Thus, intracavitary left ventricular microbubbles are often detected during cardiac operations, particularly during valve replacement, but are not predictive of postoperative neurologic complications. This is true even if microbubbles are densely concentrated; attempts to eradicate microbubbles are unsuccessful and may be unnecessary.

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The origin of central nervous system complications during open heart surgery often is not known.[1] Of the many potential causes, air embolism during cardiac surgery is particularly dreaded because this complication is often avoidable. Recently, 2-dimensional (2-D) echocardiography has been used to detect left ventricular (LV) intracavitary air by means of the distinctive sonographic appearance of microbubbles. With use of this intraoperative technique, a high prevalence of intracardiac microbubbles has been shown after cardiopulmonary bypass is discontinued.[2] Although microbubbles can be detected easily with ultrasound techniques,[3–5] their clinical significance is not known.

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We previously reported on the safety and ease of transesophageal echocardiography for obtaining high-quality cross-sectional images throughout the operative procedure.[6,7] Using this imaging modality, we determined whether the presence or absence of LV intracavitary microbubbles during cardiac surgery predicts neurologic outcome.

Methods

Before surgery, 82 patients undergoing various types of cardiac surgery (Table I) gave informed consent for intraoperative transesophageal echocardiography. After induction of general anesthesia and tracheal intubation, a flexible gastroscope with a miniature 3.5-MHz phased-array transducer at its tip (Diasonics) was introduced into the esophagus. Cross-sectional LV images were obtained at the level of the papillary muscles and the mitral valve before and immediately after cardiopulmonary bypass. The images were recorded and stop frames were reviewed in order to quantify the maximal number of LV intracavitary microbubbles per frame. Microbubbles were identified as small, oblong, highly mobile, echodense particles (Fig. 1). We used the same rating system as Rodigas et al[2]: 0 = absent, 1 = fewer than 5/frame, 2 = 10 to 25/frame, and 3 = too numerous to count (Fig. 1).

Before discontinuing cardiopulmonary bypass, when grade 2 or 3 microbubbles were identified, attempts to manually

TABLE I Detection and Grading of Microbubbles by Transesophageal Echocardiography

Operation	Grading of Microbubbles 0	1	2	3	No. of Pts
CABG	38	4	0	0	42
Valve replacement	10	6	6	8	30
CABG + aneurysm	0	0	2	1	3
ASD	0	1	1	1	3
TOF	0	0	1	1	2
PFE	0	0	0	1	1
Constrictive pericarditis	0	1	0	0	1
Extracardiac*	38	5	0	0	43
Intracardiac*	10	7	10	12	39
Total	48	12	10	12	82

* Microbubble detection significantly increased in intracardiac (29 of 39) vs extracardiac (5 of 43) procedures, $\chi^2 = 33$, $p < 0.001$.
ASD = atrial septal defect repair; CABG = coronary artery bypass grafting; PFE = removal of a papillary fibroelastoma; TOF = correction of tetralogy of Fallot.

de-air the left ventricle were made. Repetitive, direct manual LV compression was applied throughout the period immediately before termination of cardiopulmonary bypass. In patients undergoing only saphenous vein bypass grafting, no direct venting of the ventricle was performed, but all of these patients had left-sided cardiac decompression accomplished by means of the pulmonary artery.

Patients were followed prospectively for the development of any focal or generalized neurologic deficits in the prehospital discharge period. Neurologic examination was performed by either the house officer, an investigator or a consulting neurologist when appropriate. Charts were concurrently reviewed in order to ascertain the details of any neurologic complication.

Results

Immediately after cardiopulmonary bypass, microbubbles were detected in 34 of 82 patients (41%). Grade 2 or 3 LV microbubbles were detected in 22 patients (27%). None of the patients undergoing aortocoronary bypass surgery had grade 2 or 3 microbubbles and only 4 patients had grade 1 microbubbles identified. In contrast, intracardiac procedures such as valve replacement, atrial septal defect repair, LV aneurysmectomy, congenital defect repair and resection of an endocardial tumor were associated with a relative preponderance of dense microbubbles, with grade 2 or 3 present in 22 of 39 patients (56%). The other procedure included in this series was a pericardiectomy, which was accompanied by detection of grade 1 microbubbles. These results are summarized in Table I.

The incidence of microbubble detection in the immediate postoperative period was significantly higher among those undergoing intracardiac procedures compared with those undergoing extracardiac procedures: 29 of 39 patients (74%) vs 5 of 43 patients (12%), respectively ($\chi^2 = 33$, $p < 0.001$).

Intraoperatively, manual attempts to eradicate residual air were unsuccessful in all 22 patients who had grade 2 or 3 microbubbles. Success was defined as complete eradication of microbubbles. The grade was reduced by at least 1 in 13 of 22 patients in this group.

Postoperatively, neurologic follow-up data revealed no new focal deficits in any study patient. Before entry in the study, 12 patients had sustained a neurologic event, either a stroke or transient ischemic attack and 2 patients had a history of grand mal seizures. After surgery, a generalized encephalopathy, or acute confusional state,[8] was present in 7 patients and lasted from 3 to 5 days. The generalized deficit occurred in 4 of 48 patients in whom no microbubbles were detected and 3 out of 34 patients with intraoperative microbubbles (difference not significant). Detailed chart review of these 7 cases failed to reveal a clearcut origin for the

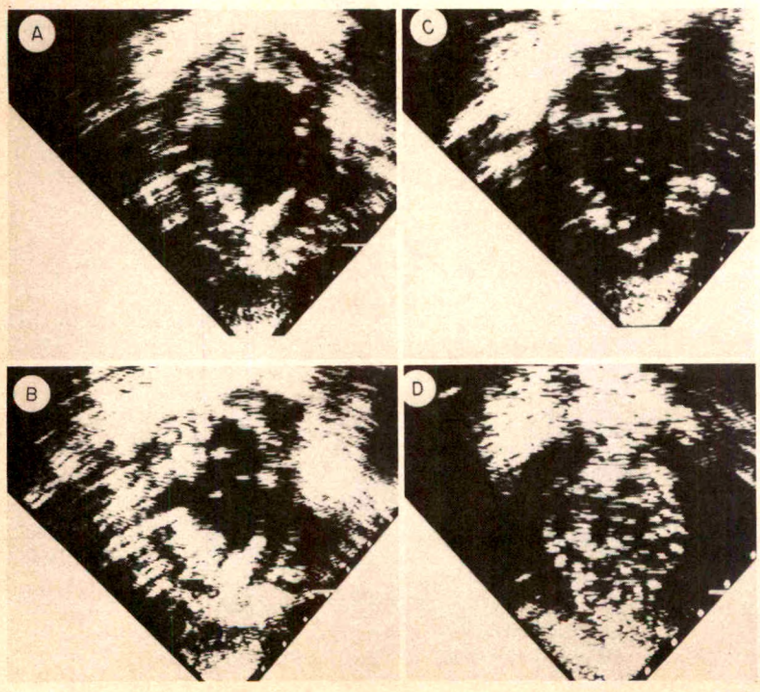

FIGURE 1. Grading of intracavitary left ventricular microbubbles in stop-frame cross-sectional echocardiograms, at the mid–papillary muscle level, recorded during cardiac surgery. Microbubbles are demonstrated as small, oblong, echodense particles within the cavity. **A,** grade 0—microbubbles are absent. **B,** grade 1—fewer than 5 microbubbles per frame. **C,** grade 2—10 to 25 microbubbles per frame. **D,** grade 3—too many microbubbles to count.

encephalopathy. Each patient had been treated with a variety of medications, anesthetic agents and transient hypotension in the 24 hours after surgery. Thus, it remains unclear whether cerebral air embolism in any way caused the generalized neurologic deterioration that occurred in these 7 patients.

Discussion

Avoidance of major central nervous system complications after cardiac surgery, which occur in approximately 5% of patients undergoing such procedures,[1,9] is an essential goal. Without question, air embolism from the LV cavity is responsible for some postoperative strokes. Using transesophageal 2-D echocardiography, we have shown that microbubbles are often detected immediately after cardiac surgery, particularly valve replacement and other intracardiac procedures. However, attempts to eradicate the microbubbles were unsuccessful and despite an extremely high density of intracavitary bubbles in some patients, gross neurologic deficits did not occur postoperatively in any study patient. Our results related to the high incidence of LV microbubbles are in agreement with those of Rodigas et al.[2] In their study, of 79 patients undergoing a variety of cardiac procedures, in 49 patients (62%) microbubbles were present, more often in valve replacement cases. In no patient did a gross neurologic deficit develop postoperatively. In contrast to their study, however, continuous transesophageal 2-D echocardiography after cardiopulmonary bypass allowed us to monitor attempts to remove the microbubbles. Furthermore, our study was designed to consider neurologic outcome and we prospectively identified 7 patients with encephalopathy, which may have been related to cerebral air embolism.

The lack of a stroke or new focal deficit in both series, despite finding high-grade intracavitary microbubbles in 26% of patients, raises the issues of the sensitivity and clinical significance of microbubble detection. The considerable body of work in the field of contrast echocardiography suggests that microcavitation or microbubbles do indeed represent air.[10–12] Certainly, the preponderance of microbubble detection after intracardiac procedures, which allow the introduction of air into the left ventricle, confirms this hypothesis.[2] If air is frequently present in the left ventricle after cardiopulmonary bypass, why aren't there more clinical sequelae observed? Several explanations are possible. First, some studies suggest that 2-D echocardiography is so sensitive in the detection of microbubbles as to lead to false-positive diagnoses. Although this would be expected for grade 1 microbubbles, it is difficult to imagine that either grade 2 or, especially, grade 3 microbubbles represent false-positive findings. Second, it is possible that air is, in fact, embolized, but these 2- to 100-μ particles[3–5] may be cleared from the circulation without significant loss of perfusion. Feinstein et al[13] showed in an experimental study that microbubble size plays a critical role in their passage through the capillary bed and that large microbubbles coalesce, temporarily obstruct flow and subsequently shrink or collapse. The third possible explanation relates to the underdiagnosis of a clinical event, in this case extremely more subtle neurologic deficits, which have not been prospectively related to microbubble embolization. This represents a limitation of the current study, which did not ascertain long-term neurologic follow-up or include specific objective psychological or cognitive testing.[14] Recent studies suggest that post–cardiopulmonary bypass neurologic damage may be subclinical.[15,16] However, no study patient evinced any focal neurologic deficit postoperatively.

Implications: Transesophageal 2-D echocardiography is safe and relatively easy to perform intraoperatively. Owing in part to its ability to detect microbubbles, it has been suggested that this technique, or direct 2-D echocardiography from the epicardial surface, be applied widely to patients undergoing not only cardiac but also neurosurgical procedures.[17–19] The present study points out that even dense intracavitary LV microbubbles so detected may not predict an adverse postoperative clinical neurologic outcome. Further, the presence of microbubbles after intracardiac procedures is not significantly affected by manual attempts to eradicate them. Such attempts may be unnecessary, because in keeping with the results of Rodigas et al,[2] no data support their clinical significance.

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Right Ventricular Ejection Fraction Measured by First-Pass Intravenous Krypton-81m: Reproducibility and Comparison with Technetium-99m

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Study of the effects of various diseases and therapeutic manipulation of pulmonary vascular resistance on the right ventricle has been restricted by methodologic limitations. The radioactive gas in solution, krypton-81m was used to study the right ventricle and the technique was compared with a technetium-99m method. In 22 subjects, first-pass krypton-81m right ventricular ejection fraction, acquired both in list mode and electrocardiogram-gated frame mode, correlated well (r = 0.81 and 0.86, respectively, p <0.01) with that determined by technetium-99m first-pass studies over a broad range of ventricular function. The reproducibility of the technique was excellent (r = 0.84 and 0.95 for each acquisition mode, respectively). Krypton-81m first-pass studies provide accurate and reproducible estimates of right ventricular function. Use of krypton allows multiple measurements, with or without perturbations, over a short period of time.

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Studies of right ventricular (RV) performance in patients with coronary artery disease,[1,2] congenital heart disease[3] and chronic obstructive pulmonary disease[4] have been performed since 1951. The proliferation of pharmacologic means to manipulate pulmonary vascular resistance with agents such as oxygen, hydralazine, nitrates and, most recently, nifedipine makes assessment of RV function timely.[5–10] Echocardiography and contrast angiography are not adequate for this application. Radionuclide methods using technetium-99m have been used to study the right ventricle,[2] but have been limited by background accumulation with first-pass methods; the presence of tracer in the left ventricle with the equilibrium method has made accurate assessment of the activity within the right ventricle difficult. We studied a new method, using intravenous krypton-81m, for assessment of RV function to obviate these difficulties.

Methods

Twenty-two subjects were studied: 7 normal volunteers, 13 patients with chronic obstructive lung disease and 2 patients with primary pulmonary hypertension. Each subject underwent multiple first-transit krypton-81m studies (see later), with injection into an antecubital vein from a rubidium-81/krypton-81m generator. The generator consisted of the parent, rubidium-81 (half-life = 4.5 hours, total activity of the generator 15 to 20 mCi), fixed on a macroporous cation exchange resin (AGMP-50 resin column). The daughter, krypton-81m (half-life 13 seconds), was eluted continuously in 5% dextrose in water (low free-ionic content) at a rate of 20 to 30 ml/min using a Masterflex rotary tube pump. A cold scavenger resin column was included between the generator and the patient to reduce the rubidium breakthrough reaching the patient to a minimum (see Radiation dosimetry section). The patients were placed in the 30° right anterior oblique position. The first transit of krypton-81m was imaged with a gamma camera with a 200-keV, parallel-hole collimator interfaced to a dedicated minicomputer. Two methods of computer acquisition were used: list mode and electrocardiogram-gated first-pass frame mode.

For the list mode technique, data collection started when the rotary pump was turned on and continued until activity reached the lungs, the approximate duration being 30 to 50 seconds. A series of images was created from the list mode data that identified the right atrium, right ventricle and pulmonary artery. The operator drew a rough region of interest around the right ventricle. A high-frequency time-activity curve (30 ms/point) was derived. End-diastole for each beat was defined as the peaks and end-systole as the troughs of the time-activity curve. A 16-frame composite cardiac cycle was created using only the frames showing activity in the right ventricle.

In the electrocardiogram-gated frame mode procedure, the acquisition was 20 to 40 seconds, beginning when activity was first noted in the superior vena cava on the persistence scope. Acquisition was terminated when activity reached the lung fields. Two regions of interest (end-diastolic and end-systolic) were used in calculating the RV ejection fraction.

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TABLE I Dose Estimates for Krypton-81m Intravenous Infusion (mrad/mCi ^{81}Rb-min)

Target Organ	Injection Site	Source Organ: Heart	Source Organ: Lungs	Total Body	Total Dose
Injection site	3.524	—	—	—	3.524
Heart	—	0.481	—	—	0.481
Lungs*	—	0.015	1.5	0.014	1.179
Active bone marrow*	—	3.9×10^{-3}	0.012	0.014	0.030
Testes*	—	4.2×10^{-5}	9.2×10^{-5}	0.011	0.011
Ovaries*	—	3.9×10^{-4}	9.2×10^{-4}	0.015	0.016
Total body*	—	9.1×10^{-3}	0.025	0.014	0.048

* Includes ^{81}Rb breakthrough of 0.15 μCi/mCi ^{81}Rb-min.
— = not computed.

End-diastolic, end-systolic, and background-count regions of interest were drawn with the assistance of phase and amplitude images. Ejection fraction was calculated as [(RVED − RVES)/RVED] × 100 where EF = ejection fraction, RVED = the background-corrected counts in the end-diastolic region of interest, and RVES = the background-corrected counts in the end-systolic region of interest.

Each subject underwent 1 list mode and/or 1 gated frame mode study and at least 1 replicate study of each technique within 2 to 3 minutes of the first acquisition. In 17 patients, repositioning between acquisitions was performed by deliberately moving the patient out from the camera to test the limits of reproducibility.

Each patient underwent a first-pass technetium-99m pertechnetate (15 to 20 mCi) study in the right anterior oblique 30° position within 24 hours after the krypton-81m studies.

Radiation dosimetry: The assumptions were for conservative dose estimation. The generator was assumed to be eluted with an efficiency of 90% and free of radionuclidic impurities. Transit time from generator to infusion site was assumed to be 5 seconds, yielding a total correction factor for activity delivered of 0.689. No correction for decay during vascular transit in vivo was used. Krypton-81m activity was assumed to be eluted at rate of production. Therefore, including the branching of rubidium-81 to krypton-81, the production/elution rate was 51.1 μCi of krypton-81m per millicurie of rubidium-81 per second. The corrected delivery rate was then 2.11×10^3 μCi of krypton-81m per millicurie of rubidium-81m per minute of infusion. At the infusion site, blood and infusate were assumed to be instantaneously mixed. Assuming blood flow at the infusion site to be 760 ml/min, the instantaneous activity concentration was then 2.93 μCi/ml/mCi of rubidium-81. All infused activity was assumed to enter the lung by way of pulmonary circulation. For organ exposure estimation, recirculation was ignored, whereas for total body exposure, 2% of the administered activity was assumed to remain in circulation. Effective washout halftimes for lung and whole body were assumed to be 9 and 13 seconds, respectively.

The dose values are listed in Table I. The rubidium generator was typically 15 to 20 mCi.

Infusion times were usually 30 seconds (maximum 1 minute). This gives a typical dose of about 50 mrads to the infusion site and less than 18 mrads to lung and 8 mrads to heart per first-pass study. For assessment of the radiation exposure from rubidium-81 "breakthrough" in intravenous administration of krypton-81m, it was assumed (worse case) that for a 15-mCi generator and 300 ml of eluent delivered, the total rubidium-81 activity administered was 45 μCi. The assumption was based on measured breakthrough ranging from 0.1 to 4.2 μCi/100 ml eluent for generators 5 to 20 mCi in size. Assuming instantaneous uptake, uniform distribution whole body, and no biologic elimination, radiation doses from rubidium-81 were computed using "S" factors.[11–14] Dose estimates also included contribution from daughter krypton-81m. Typical dose estimates of breakthrough (for flow rate 30 ml/min) for a minute first-pass study are listed in Table II. For this preliminary study, a cold resin column was positioned in the infusion line to preclude any rubidium-81 breakthrough from reaching the patient. However, these dose estimates showed that this precaution is probably not necessary for the use of this generator for dose reduction and may serve only as a "worst case" downstream trap in the unlikely event of severe resin breakthrough (as in an accidental elution with NaCl, which would strip the column).

TABLE II Dosimetry Breakthrough for Typical Study*

Organ	Total Dose
Testes	0.4 mrad
Ovaries	0.64 mrad
Active marrow	0.57 mrad
Total body	0.58 mrad

* Assuming 4.5 μCi rubidium-81/30 ml eluent.

Results

A typical study of RV ejection fraction is shown in Figure 1. The data were analyzed as follows (Fig. 2–4): (1) list mode acquisition of krypton-81m vs list mode for technetium-99m pertechnetate; (2) gated frame mode krypton-81m vs list mode technetium-99m pertechnetate; (3) correlation between krypton replicates for all subjects; (4) correlation between list mode or gated frame mode krypton replicates using only studies with repositioning; and (5) krypton list mode vs gated frame mode.

The correlation and the number of data pairs for the different methods of analysis are listed in Table III. The mean of all replicates (33 for list mode; 30 for frame mode) for each patient was used for correlation with technetium-99m pertechnetate RV ejection fraction. The list mode and gated frame mode krypton-81m techniques agreed equally well with the technetium-99m RV ejection fraction ($r = 0.81$, $p < 0.01$, Fig. 2 left, and 0.86, $p < 0.01$, Fig. 2 right, respectively).

The 99% confidence intervals are shown about the regression lines in Figure 3 for the plot of the list mode krypton-81m vs gated frame mode results for all patients who had both studies; the results are averaged over replicates for each technique. The correlation was excellent ($r = 0.88$, $p < 0.01$).

For each mode we assessed the reproducibility by presenting the correlation between pairs of measurements, each pair from a different subject. Because each

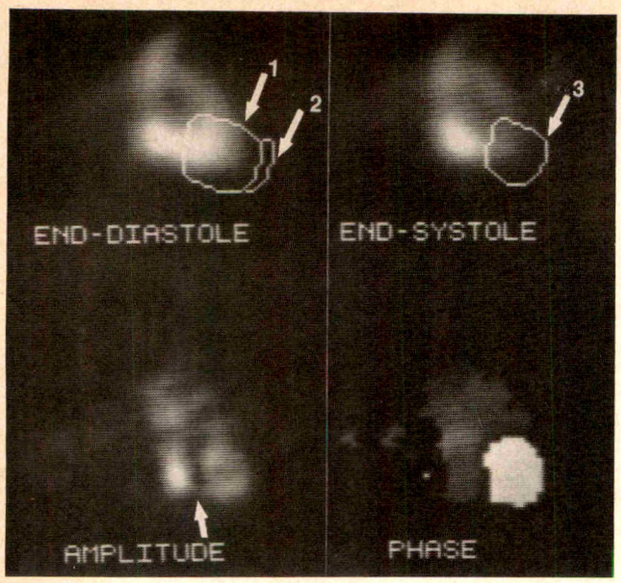


FIGURE 1. Composite of first-pass processed images. **Top left,** composite end-diastolic image created from a first-pass study. The activity outlines the superior vena cava, right ventricle and pulmonary outflow tract. **Arrow 1** marks the region of interest taken for end-diastolic counts. **Top right,** composite end-systolic image. **Arrow 2** marks the background region of interest. **Arrow 3** marks the region of interest for end-systolic counts. **Bottom left,** the Fourier amplitude image. **Arrow** denotes the value plane separating the right atrium and right ventricle. A similar separation is noted in the phase image. Both phase and amplitude images are used to help define the regions of interest.

TABLE III Correlation Coefficients (r) for Right Ventricular Ejection Fraction Estimates

Comparison	No. of Pts.*	r
Avg. Kr LM vs Tc	14	0.81 (0.18)†
Avg. Kr FM vs Tc	15	0.86 (0.15)†
Avg. Kr FM vs GFM	10	0.88 (0.16)†
Kr LM all replicates	14	0.95‡ (0.89–0.99)§
Kr FM all replicates	12	0.99‡ (0.96–0.99)§
Kr LM repositioning replicates	12	0.95‖
Kr FM repositioning replicates	5	0.98‖

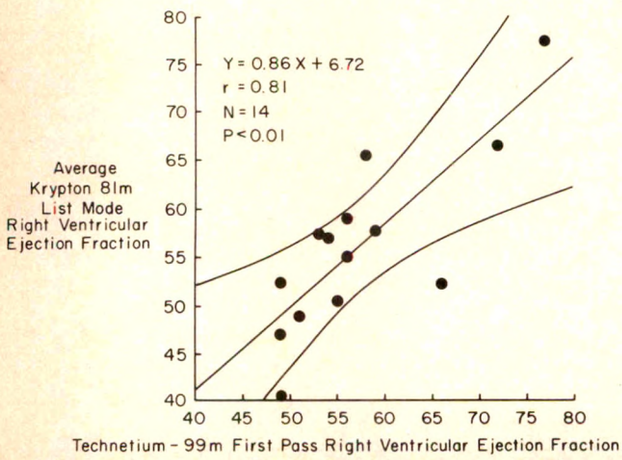
* The actual number of averaged observations is in the text.
† Standard error of slope of linear regression.
‡ Mode of histogram in Figure 4.
§ Confidence limits on correlations.
‖ $p < 0.05$.
Avg. = average; FM = frame mode; GFM = gated frame mode; Kr = krypton-81m first-pass right ventriculogram; LM = list mode; Tc = technetium-99m.

subject had multiple measurements (38 for list mode, 22 for frame mode), we used a randomization method to construct a distribution of correlation coefficients: From the data on each subject, we randomly selected 1 pair of measurements and computed the correlation coefficient for all subjects. This procedure was repeated 1,000 times. The histogram (Fig 4) of correlation coefficients was used to define the 95% confidence limits on the reproducibility correlations (Table III and IV). The correlations in the 17 patients for whom a single camera-repositioning replicate was available are listed in Table III.

The paired replicates for all possible combinations are shown in Figure 3 for the list mode and the gated frame mode techniques. There was excellent reproducibility, even when correlation of replicates was limited to those with repositioning (Table III, r = 0.95 and 0.98, respectively). The average coefficients of variation over all patients for each technique of acquisition (4.5% and 3.2% for list mode and gated frame mode, respectively) are listed in Table IV, confirming the excellent reproducibility of both techniques.

Discussion

Early studies to evaluate RV performance used indicator dilution techniques, including dye,[15] thermal[16] and radionuclide[17] methods. Contrast ventriculography has been used since 1967 to obtain RV volumes.[18] However, contrast angiography must rely on various geometric models of RV shape,[19] and requires correction by regression equations for systematic overestimation



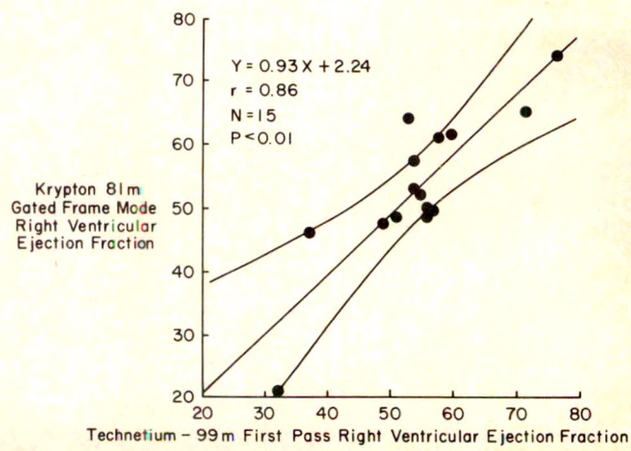


FIGURE 2. Comparison of the 2 krypton-81m acquisition methods with the technetium-99m pertechnetate method. The krypton estimates were averaged for a given patient. The linear regression line was plotted with 99% confidence limits. **Left,** average krypton-81m list mode right ventricular ejection fraction vs technetium-99m list mode right ventricular ejection fraction. The correlation between the average krypton and technetium pertechnetate estimates of right ventricular ejection fraction is 0.81 ($p < 0.01$). **Right,** average krypton first-pass electrocardiogram-gated frame mode right ventricular ejection fraction vs technetium-99m list mode right ventricular ejection fraction.

of RV volume. Because of the difficulty of geometric modeling and the invasive nature of angiography, study of the right ventricle with this method has been of little value in adults.

Echocardiography has had limited usefulness in study of the right ventricle. M-mode echocardiography cannot fully delineate the irregular shape of the right ventricle because of the small area sampled by this technique.[20,21] No specific geometric model has been predictive of volume from the axes measured by 2-dimensional echocardiography.[21]

Several methods have been developed using gated blood pool techniques.[22] The use of slant-hole collimator has been advocated as a refinement of the equilibrium method.[23] However, with all of these methods, the underlying assumption has been that overlap of the right ventricle with the right atrium was not significant.

Steele et al[24] used first-pass technetium-99m to measure ejection fraction. This method had a correlation of 0.8 with contrast angiography,[25] and has remained the standard method of assessing performance in most clinics. To obtain repeat studies using first-pass techniques, Berger et al[26] used rapidly cleared technetium ligands. However, accumulation of background activity limited the number of first-pass studies that could be obtained in a single sitting. Radiogold-195m has also been used similarly. It is not eliminated by the lungs, and thus appears in the left ventricle, which interferes with RV study.[27] The use of radioactive gases that clear rapidly from the lungs for first-pass measurement of RV ejection fraction has the advantage of little background accumulation and isolation of the radionuclide to the right side of the heart. Goldberg et al[28] showed good agreement of intravenous xenon with technetium-99m first-pass studies. Krypton-81m has the additional advantage of a 13-second half-life, allowing rapid clearance of isotope, resulting in low radiation exposure and background activity. Knapp et al[29] performed list mode intravenous krypton studies of the right ventricle, but did not validate the accuracy of the method.

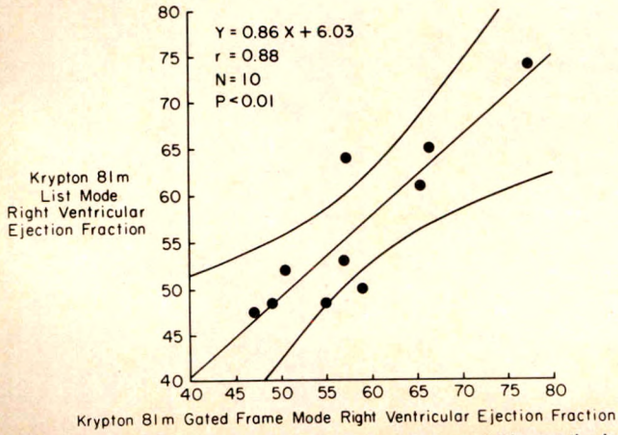


FIGURE 3. Comparison of both krypton computer acquisition methods. In 10 patients in whom both list mode and gated frame mode studies were obtained, the average right ventricular ejection fraction for the gated frame mode vs the list mode is plotted.

TABLE IV Reproducibility

Acquisition	No. of Pts.	No. of Studies	Average Coefficient of Variation	1 SD
LM	14	37	4.55	3.62
FM	12	28	3.23	1.96

* CV = (SD/mean) × 100% for each patient.
FM = gated frame mode; LM = list mode; SD = standard deviation.

We found good correlation between the krypton-81m and technetium-99m pertechnetate first-pass studies. The correlation was equally good for krypton studies acquired by list mode or electrocardiogram-gated frame mode. Both acquisition techniques have advantages and limitations. The list mode allowed selective beat-to-beat determination of RV ejection fraction. List mode was operator-independent, in that precise timing of start and termination of acquisition was not necessary. In gated frame mode, however, accurate timing of the transit to the pulmonary artery was required to exclude the pulmonary phase from the present framing sequence. Because the list mode in this study did not include the R wave from the electrocardiogram, the linkage of the R wave to the gated frame mode allowed exact identification of the end-diastolic frame, whereas the list mode method used the peaks of the time-activity curve. The gated frame mode technique was somewhat more technically reliable for krypton studies (91% for gated frame mode vs 74% success for list mode). Frame mode required less computer space and processing time than list mode.

The excellent reproducibility and rapid repeatability with krypton were a result of prompt removal of tracer by the lungs, the short half-life, and rapid regeneration of the daughter by the parent generator. The method was easily performed and highly reproducible even after repositioning. Rapid regeneration of activity in the generator allowed replicate acquisitions every 1 to 2 minutes.

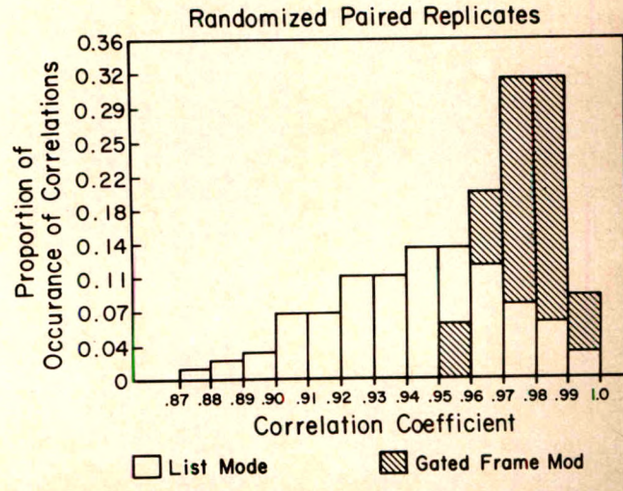


FIGURE 4. Reproducibility studies. The result of randomly pairing replicates is shown as histograms of correlation coefficients. The peak distribution of the gated frame mode (**hatched bars**) is slightly higher (r = 0.98) than the list mode (**open bars**) peak correlation (r = 0.95).

The radiation dose from first-pass krypton was small compared with first-pass technetium-99m pertechnetate (Table I). Even for 10 replicate studies, radiation dose was low, with the maximal dose to the skin at the intravenous site, which is a radioresistant area.

The only inconvenience of intravenous krypton was the short half-life of the parent, rubidium-81 (4.5 hours), limiting useful generator lifespan to 1 day. However, rubidium-81 is cyclotron-produced for ventilation generators in the U.S. 5 days a week, and could become more available for intravenous use in the future. The imaging characteristics of krypton-81m were excellent (photopeak 190 keV), allowing use of a medium-energy (or high-rated, low energy) collimator increasing count-density information without significant loss of resolution. The high energy level of radiogold-195m is not well suited to gamma camera imaging, and requires a high-energy collimator, which decreases resolution significantly.

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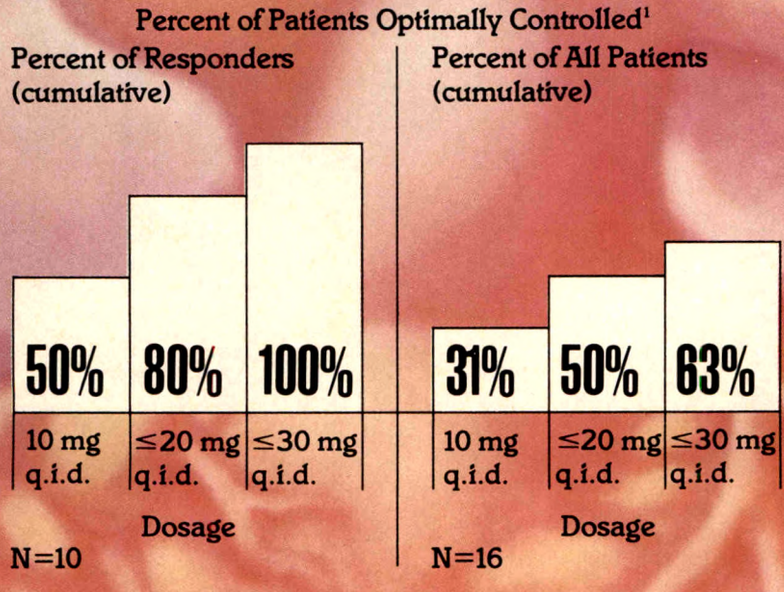

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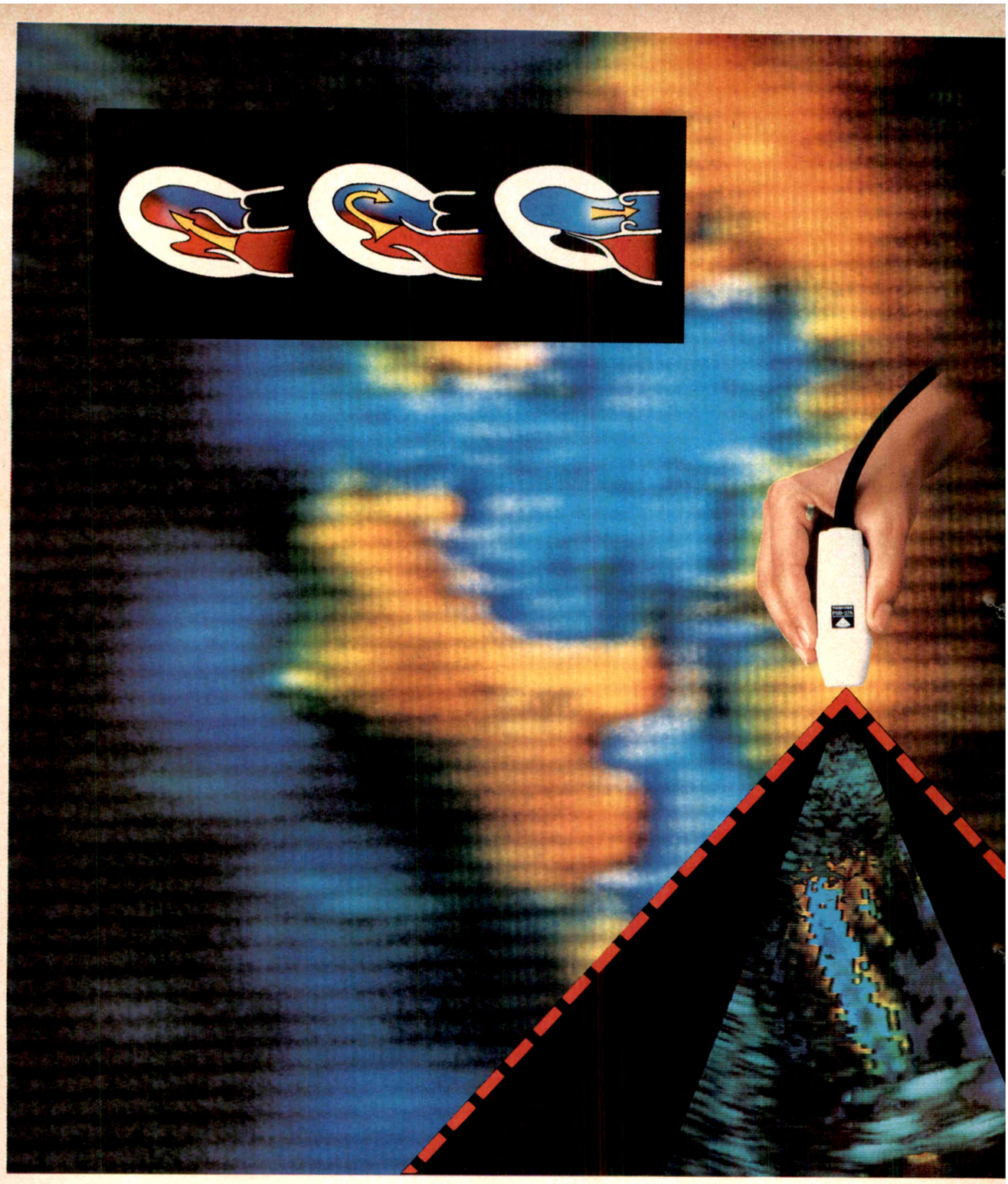

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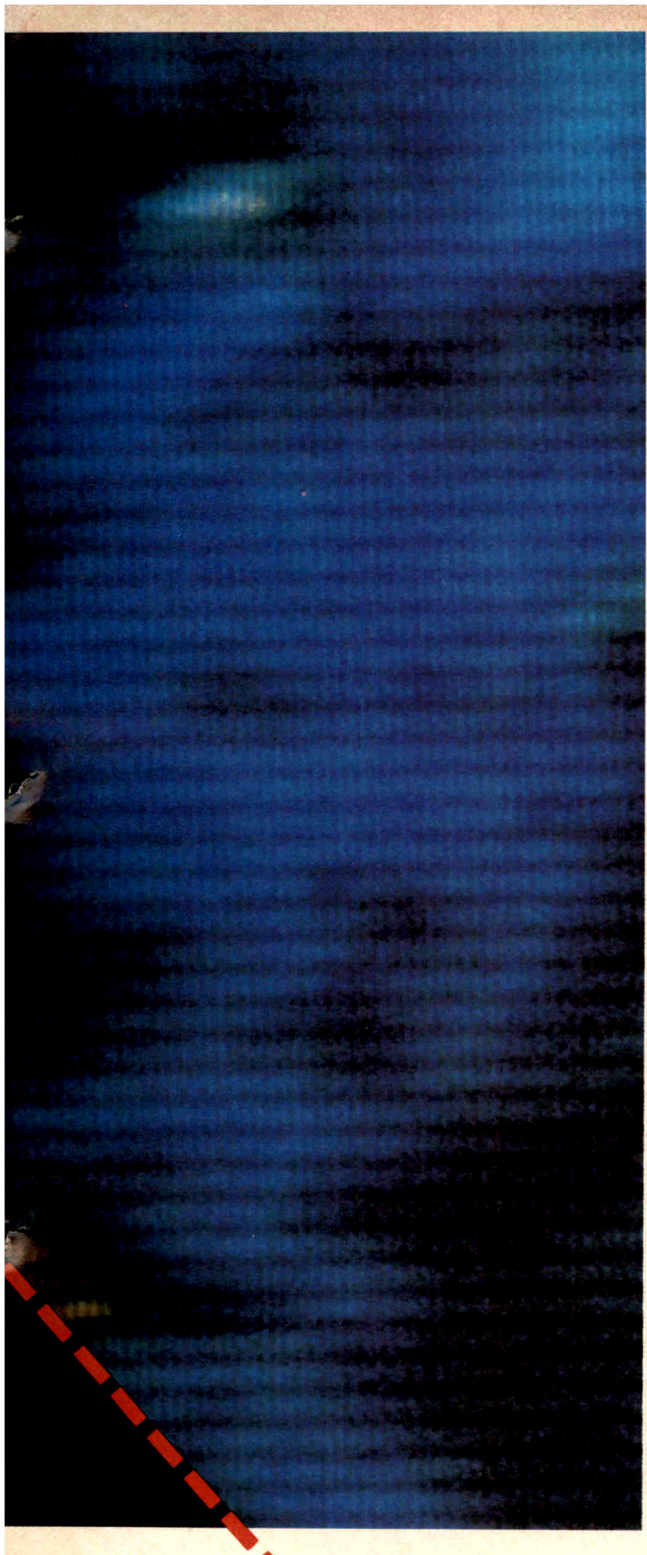

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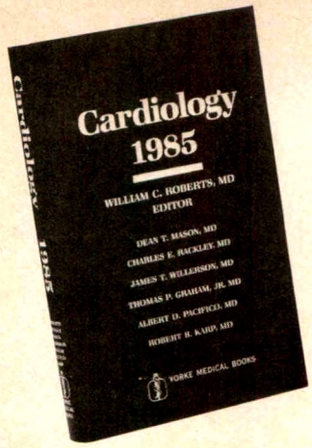

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Measurement of Left Ventricular Volume Using Single-Photon Emission Computed Tomography

GARY R. CAPUTO, MD, MICHAEL M. GRAHAM, PhD, MD, KIRK D. BRUST, BS, J. WARD KENNEDY, MD, and WIL B. NELP, MD

A count-based method for measuring left ventricular (LV) volume using technetium-99m-labeled red cells and ungated single-photon emission computed tomography is described. The tomographic slices were used to determine the counts per milliliter in the center of the left ventricle and total LV counts, which were used to derive mean LV volume. End-diastolic and end-systolic volumes were calculated from the mean volume using the LV time-activity curve from planar gated blood pool images. Phantom evaluation with simulated LV volumes (50 to 400 ml) in air, in a phantom filled with water, with 10% background, and with a simulated right ventricle, showed excellent accuracy. For clinical validation, 30 patients underwent electrocardiographically gated planar and nongated tomographic acquisition of the cardiac blood pool followed by single-plane cineangiography. For end-diastolic and end-systolic volumes combined, the correlation with cineangiography showed a standard error of the estimate (SEE) of 24 ml and 14 ml, respectively. Mean intra- and interobserver deviation was 12 ml and 14 ml (SEE 13 ml and 16 ml), respectively. It is concluded that this noninvasive count-based technique, requiring no assumptions regarding LV geometry, is an accurate and reproducible way to measure LV volume.

(Am J Cardiol 1985;56:781–786)

Left ventricular (LV) volume is an important measurement in the evaluation of cardiac function. Radiographic LV cineangiography is the standard method for measuring LV volume.[1,2] This method assumes the left ventricle to be a prolate ellipsoid, which may not be true in patients with regional LV dysfunction.[3] Furthermore, it is invasive, requiring intraventricular contrast injection, and is not suitable for serial volume determination. These limitations have resulted in a search for an accurate and reproducible noninvasive method for measuring LV volume. Such a method would be useful for monitoring serial changes in cardiac function and evaluating the effects of cardiac surgery and drug therapies.

M-mode echocardiography may be used to measure end-diastolic and end-systolic internal dimensions of the left ventricle. These dimensions have been used to estimate LV volume[4,5]; however these volumes may be inaccurate owing to the many assumptions required to obtain a 3-dimensional volume using a single internal dimension.[5]

Several investigators have attempted to use 2-dimensional echocardiography to calculate LV volume.[6–12] Among these approaches is the area-length technique, often used for angiographic volumes. How useful these approaches are in various pathophysiologic states remains to be determined.

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Radionuclide first-pass and gated blood-pool LV volume determinations have been made using the same basic area-length method.[13–16] Although some of the limitations inherent in contrast ventriculography are avoided, precise definition of the left ventricle is difficult, and the same geometric problems remain. Any technique that attempts to calculate LV volume from data that are not 3-dimensional has limitations.

An alternate radionuclide approach is count-based analysis of planar gated blood-pool images, thus avoiding the geometric problems.[16–23] However, this method requires correction for photon attenuation, and superimposed vascular structures may contribute extraneous counts to the left ventricle.[24]

Although transmission computed tomography provides 3-dimensional cardiac data that have been used to measure LV casts,[25] conventional scanners require contrast enhancement and exposure times that may be too long for the determination of end-diastolic and end-systolic volumes in vivo.[26]

Single-photon emission computed tomography (SPECT) obviates the problem of overlying structures and should be applicable to either the geometric or count-based method for determining LV volumes.[27]

This report examines a count-based emission tomographic approach to the measurement of LV volume and extends previous work[28] with phantoms to a validation study in a series of 30 patients.

Methods

Spatial calibration: A Lucite® phantom with orthogonal point sources was used for spatial calibration. The phantom was imaged tomographically and the distance between the

points was measured using the count profiles to clearly show the location of the center of the points. These distances were used to precisely measure the voxel size in centimeters (0.68 × 0.68 × 0.66), yielding 0.305 ml per voxel.

Simulated left ventricular chamber and torso phantom: A calibrated syringe connected to a water reservoir containing 2.5 μCi/ml of technetium-99m (Tc-99m) was used to fill an ellipsoidal latex balloon used to simulate the LV chamber, in 50-ml increments from 50 ml to 400 ml. The torso phantom was a cylindrical water bath 15 cm in diameter. A similar biventricular torso phantom included an elongated 100-ml simulated right ventricular chamber separated from the LV chamber by a 1-cm-thick simulated ventricular septum.

Tomographic images: Tomographic images of the simulated LV chamber were recorded in air, in the torso phantom filled with water, water with 10% background activity by volume, and water with 10% background activity and the addition of a simulated right ventricle. The long axis of the torso phantom was parallel to the axis of rotation of the gamma camera.

For each volume measurement, images were acquired over 360° in 64 five-second increments using a GE 400A camera mounted on a 400T stand interfaced to an ADAC System 1 computer, using a 64 × 64 matrix and word mode. Preliminary ADAC software (obtained from CGR) was used for non-attenuation-corrected image reconstruction. This software provided filtered, back-projected images, but did not allow specification of the filter or attenuation correction.

Simulated left ventricular chamber volume determination: For each tomographic slice a region of interest encompassing the edge of the activity within the simulated LV chamber was defined using a light pen. The counts contained within each region of interest were measured in each slice and then summed to yield the total counts in the LV chamber. After spatially smoothing a midventricular chamber slice twice with a 9-point binomial filter, the maximal count per voxel within the region of interest was determined. This was assumed to be the count per voxel of Tc-99m at the depth of the simulated LV chamber. Using the previously determined spatial calibration factor and this count, the count per milliliter of Tc-99m solution was calculated. The simulated LV chamber volume was obtained by dividing the total counts contained in the simulated LV chambers by the count per milliliter.

Data acquisition and analysis: Data were obtained with the simulated LV chamber in air, in the torso phantom filled with water, water with 10% background activity by volume, and water with 10% background activity and the addition of a simulated right ventricle. In each case, calculated volumes were compared to the directly measured simulated LV chamber volumes and subjected to statistical analysis by linear regression.

Patients: Thirty-five patients, 30 with coronary artery disease, 2 with cardiomyopathy and 3 with valvular heart disease, underwent planar gated blood pool studies, followed by nongated tomographic acquisition of the cardiac blood pool. Twenty-two patients were men, mean age 54.6 years (range 23 to 73), with a mean height of 176.7 cm (range 160 to 188) and mean weight of 81 kg (range 55 to 104). Thirteen patients were women, mean age 60.5 years (range 38 to 72), with a mean height of 160.2 cm (range 151 to 169) and mean weight of 69 kg (range 52 to 86). The overall mean age was 56.8 years (range 23 to 73), mean height 170.6 cm (range 151 to 188) and mean weight 76.6 kg (range 52 to 104).

Five patients with coronary artery disease had technically inadequate LV cineangiograms after successful tomographic determination of their end-diastolic and end-systolic volumes and were not included in the data analysis. Seventeen patients had 1 or more areas of asynergy at rest, 9 of whom had at least 1 akinetic segment.

The average elapsed time from completion of tomographic acquisition to LV cineangiography was 2.8 hours (range 0.5 to 17). One patient underwent LV cineangiography 4 hours before tomographic acquisition.

Planar gated blood pool acquisition and analysis: Each patient received 25 mCi of in vitro labeled autologous red blood cells. A standard multigated acquisition of 90% of the RR interval was then performed in an optimized left anterior oblique projection using a GE 400A camera and an ADAC 3300 computer. A standard edge detection algorithm was used to create LV regions of interest for each of the 16 frames per cardiac cycle. These regions of interest were used to generate a time-activity curve for the left ventricle. This time-activity curve was corrected to 100% of the RR interval by interpolation of points during diastasis. From the time-activity curve, the ratios of the end-diastolic and end-systolic counts to the mean LV counts were determined.

Tomographic acquisition, reconstruction and analysis: After the gated planar study, 128 ten-second, nongated tomographic images were acquired over 360° with a total acquisition time of 22 minutes. The data were collected in word mode using an ADAC 3300 computer system in a 64 × 64 matrix. The images were spatially smoothed and high-speed tomographic reconstruction of the images was performed using ADAC software and a Butterworth filter with a cutoff frequency of 0.5 cycles per pixel, a filter order of 5, and a reconstruction matrix of 64 × 64. Tomographic reconstruction required 7½ minutes. The tomographic slices were orthogonal to the long axis of the patient's body and were not reoriented.

To avoid bias, the studies were coded so that the observers had no knowledge of the patient's identity at the time of analysis. Using a light pen, 2 observers independently created regions of interest encompassing the activity contained within the left ventricle for each LV slice. The mitral valve plane was approximated by defining a point at the junction between the muscular portion and the membranous portion of the ventricular septum. From this point, a line perpendicular to the interventricular septum intersecting the free wall of the left ventricle was drawn. This LV boundary was extended along both the ventricular septum and free wall, circling the apex to complete the region of interest (Fig. 1). A midventricular slice was spatially smoothed twice, using the standard 9-point binomial filter and the maximal count per pixel was taken as the count per voxel. The count per milliliter of blood was then calculated using the spatial conversion factor obtained previously. The counts from each LV region of interest were summed to yield the total counts obtained within the left ventricle. The total counts within the left ventricle were divided by the count per milliliter of blood to determine the mean LV volume.

Left ventricular end-diastolic and end-systolic determination: End-diastolic and end-systolic volumes were derived using the planar LV time-activity curve data. The end-diastolic volume is the mean tomographic LV volume times the ratio of the end-diastolic counts to the mean counts of the time-activity curve. In similar fashion, the end-systolic volume is the mean tomographic LV volume times the ratio of the end-systolic counts to the mean counts. The tomographic determination of both the end-diastolic and end-systolic volumes, including the smoothing and tomographic reconstruction, required the observer to be seated at the computer console for 11 minutes. Processing of the entire study was completed within 30 minutes.

Left ventricular cineangiography: Single-plane LV cineangiography was performed in the 30° right anterior oblique view using a pigtail catheter positioned in the body

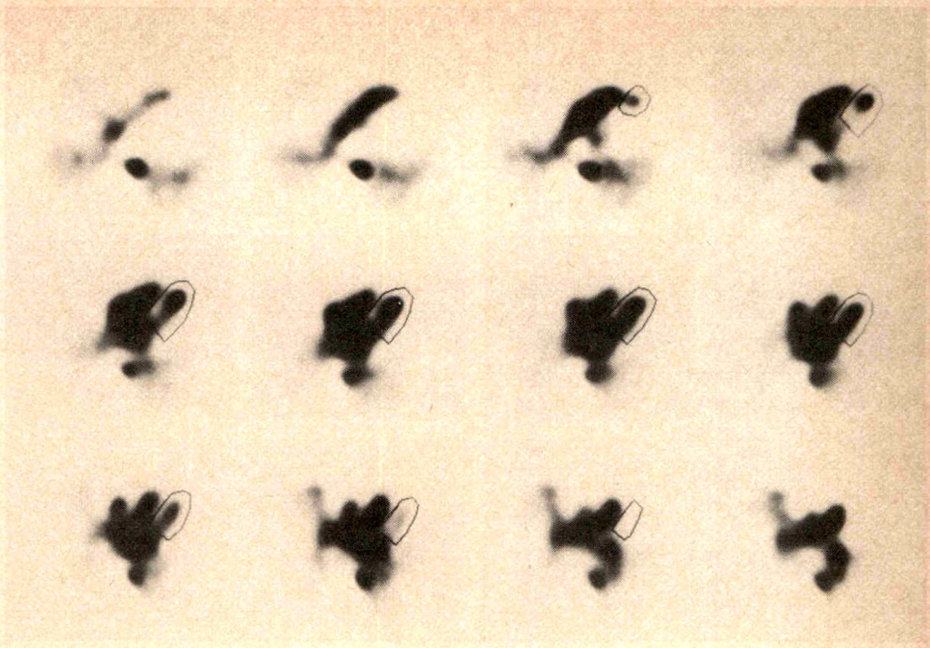

FIGURE 1. Left ventricular regions of interest for each slice. Precise localization of the endocardial surface is unnecessary.

of the left ventricle and filmed at 60 frames/s. Left ventriculograms were analyzed by a third observer by manually digitizing the end-diastolic and end-systolic frames using a VAX 750 computer according to the method of Dodge et al[1] and regression equation of Kennedy et al.[29]

For each patient in whom a technically adequate cineangiogram was recored, each observer's emission tomographically determined end-diastolic and end-systolic volumes were compared with those determined by LV cineangiography and with each other and subjected to statistical analysis by linear regression.

Results

Figure 2 is a plot of the calculated volumes of the simulated LV chamber in air vs directly measured volumes. Figure 3 is a plot of the calculated volumes of the simulated LV chamber in the torso phantom filled with water vs directly measured volumes. The addition of scattering material did not affect the accuracy of volume measurement significantly.

Figure 4 is a plot of the calculated volumes of the simulated LV chamber in the torso phantom filled with water with 10% background activity by volume vs directly measured volumes. The contribution by background counts did not affect the accuracy of volume measurement significantly. Figure 5 is a plot of calculated volumes of the simulated LV chamber in the torso phantom filled with water with 10% background activity and the addition of a simulated right ventricle vs directly measured volume. Neither scatter nor the contribution by right ventricular or background counts

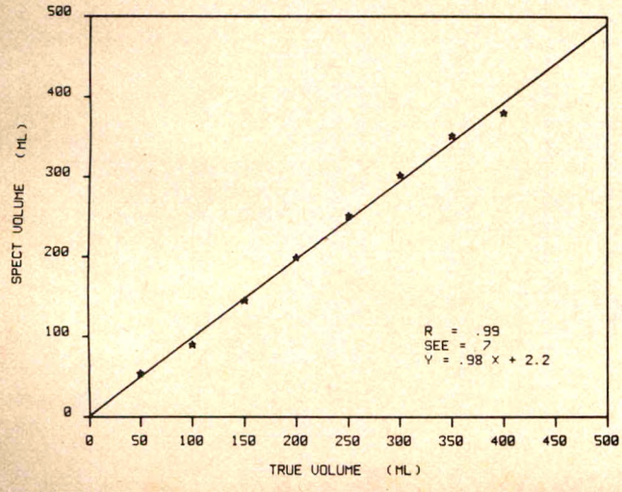

FIGURE 2. Volumes of the simulated left ventricular chamber in air determined using the count-based method compared with directly measured volumes. SPECT = single-photon emission computed tomography.

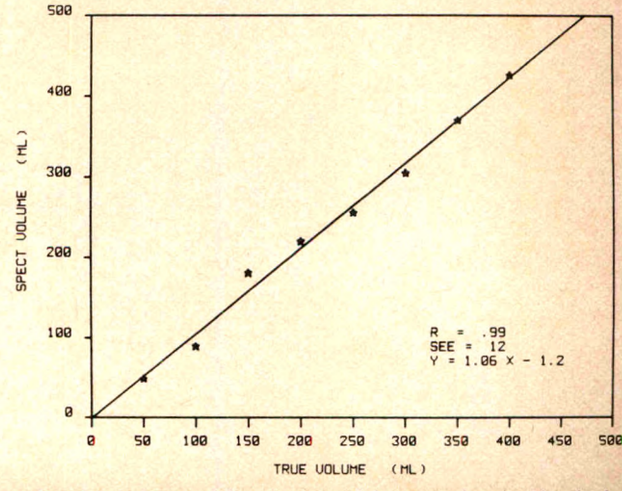

FIGURE 3. Volumes of the simulated left ventricular chamber in the torso phantom filled with water determined using the count-based method compared with directly measured volumes. SPECT = single-photon emission computed tomography.

decreased the accuracy of the measurement of simulated LV chamber volumes.

Figure 6 is a plot of LV end-diastolic and end-systolic volumes for the 30 patients with technically adequate LV cineangiograms, calculated by the first observer using the count-based emission tomographic approach vs those determined by an independent observer using cineangiography. Figure 7 is a plot of the LV end-diastolic and end-systolic volumes calculated by the first observer using the count-based emission tomographic approach against a second independent determination by the same observer. The mean deviation was 12 ml yielding good intraobserver reproducibility.

Figure 8 is a plot of LV end-diastolic and end-systolic volumes calculated by a second independent observer using the count-based emission tomographic approach against those determined by the first observer. The mean deviation was 14 ml, yielding good interobserver reproducibility.

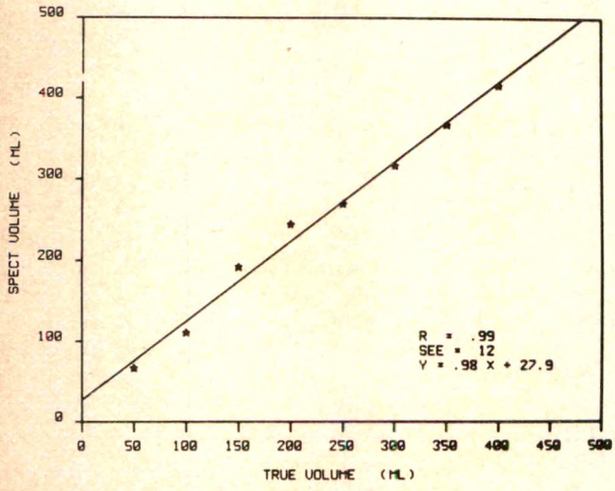

FIGURE 4. Volumes of the simulated left ventricular chamber in the torso phantom filled with water plus 10% background by volume determined using the count-based method compared with directly measured volumes. SPECT = single-photon emission computed tomography.

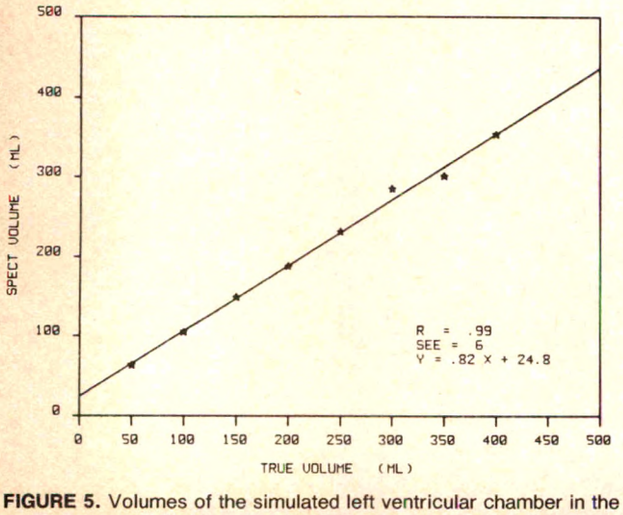

FIGURE 5. Volumes of the simulated left ventricular chamber in the torso phantom filled with water with 10% background activity by volume and a simulated right ventricle, determined using the count-based method compared with directly measured volumes. SPECT = single-photon emission computed tomography.

Discussion

LV volume is an important variable in the assessment of cardiovascular physiology and pathophysiology.[30–33] The historic standard for the measurement of LV volume has been the biplane area-length method of Dodge et al.[1]

Most adult catheterization laboratories perform single-plane left ventriculography in the 30° right anterior oblique projection, after which LV volumes are calculated by the area-length method. The studies of Kennedy et al[29] and Wynne et al[34] showed that the calculated volumes are consistently larger than the biplane volumes by as much as 20%, necessitating the use of regression equations to improve their accuracy. Kennedy, using the regression equation $y = 0.81x + 1.9$ ml, compared the resulting single-plane 30° right anterior oblique volumes with those obtained from simultaneous biplane studies. He found a correlation coefficient of 0.97 and a standard error of the estimate of 22 ml for end-diastolic volume, a correlation coefficient of 0.96 and a standard error of the estimate of 17 ml for end-systolic volume, and a correlation coefficient of 0.97 with a standard error of the estimate at 24 ml for end-diastolic and end-systolic volumes combined.

Hillis et al[35] found in a large series of patients that LV volumes can be measured accurately with single-plane angiography in a 30° right anterior oblique projection using the area-length method of Dodge et al[1] and the regression equation of Kennedy et al[29] in patients with normal as well as depressed global LV function. However, single-plane LV volumes cannot be measured reliably in patients with marked segmental wall motion abnormalities, because the geometric assumptions on which the area-length method is based are probably no longer valid.[35]

Dodge et al[36] investigated the intraobserver and interobserver variability of the area-length method using

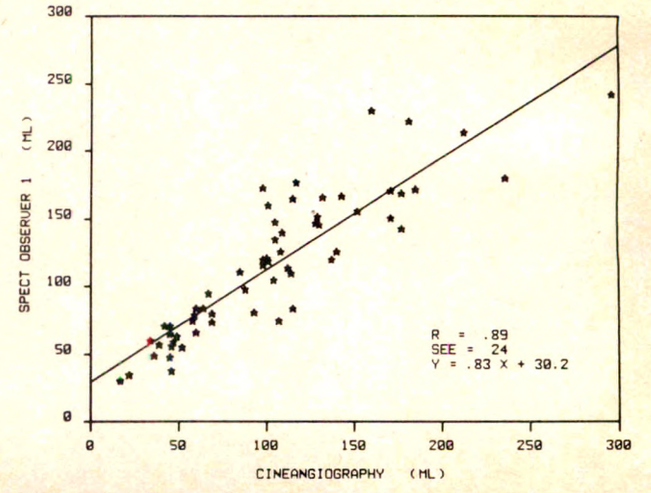

FIGURE 6. Left ventricular end-diastolic and end-systolic volumes compared with those measured by cineangiography. SPECT = single-photon emission computed tomography.

single-plane 30° right anterior oblique cineangiograms and the Kennedy regression equation. They found an intraobserver variability of 3.3 ± 3.4 ml (2.2% ± 2.0%) for end-diastolic volume and 3.2 ± 2.7 ml (5.8% ± 4.1%) for end-systolic volume, with interobserver variability of 6.6 ± 4.9 ml (4.3% ± 3.7%) for end-diastolic volume and 5.9 ± 5.3 ml (10.3% ± 10.8%) for end-systolic volume.

In considering the accuracy of SPECT end-diastolic and end-systolic volumes, it must be recognized that the comparison is being made to a single determination of the volume measured by cineangiography using a single heartbeat. Because emission tomographic volumes are derived from a mean volume acquired from approximately 1,500 cardiac cycles and the time-activity curve is derived from approximately 500 cardiac cycles, the volumes represent the mean end-diastolic and end-systolic volume during the acquisition period.

The tomographic end-diastolic and end-systolic volumes may be different from the volumes measured during the single angiographic beat, because the papillary muscles may influence volume estimates derived from analysis of the silhouette of the left ventricle, which would be more pronounced at end-systole. Patients may not be in a baseline state during the angiographic procedure. Sedatives, which may alter the patients' physiologic state, are routinely used during cardiac catheterization. Since coronary arteriography was performed before left ventriculography, the hyperosmolar contrast agent may have caused a mild increase in the blood volume, raising preload before left ventriculography. Intraventricular injection of the contrast agent begins to produce hemodynamic changes after approximately the sixth beat after injection, causing an increase in LV volume.[37] LV segmental wall motion abnormalities may have led to inaccurate cineangiographic values for end-diastolic and end-systolic volume.[35]

When comparison is made with LV cineangiography, the standard errors suggest that this emission tomographic count-based approach for the measurement of LV volume is relatively accurate and highly reproducible. The method is simple to perform and affords markedly improved counting statistics and shorter acquisition times than techniques using gated acquisition. The serious problems associated with assumptions regarding LV geometry, which may lead to inaccurate cineangiographic values for end-diastolic and end-systolic volume, are obviated.

This approach is conceptually similar to the planar count based methods, first reported by Slutsky et al.[18] The essence of the planar count-based method is that the LV count, determined from a left anterior oblique gated blood pool study, divided by the count per millilter of peripheral blood, should yield the volume of the left ventricle. The difficulties associated with this approach are that background subtraction and attenuation correction are necessary. In addition, counting efficiency correction must be done because often the blood sample is counted with different efficiency than the left ventricle.

Attenuation correction appears to be the major problem. Several approaches have been attempted using internal standards, such as an esophageal source,[20] the transverse aorta,[21] and a bolus in the right atrium,[22] or by measuring the distance from the center of the left ventricle to the chest wall.[23,24] Each group of investigators can show that their technique is reasonably accurate, but their approaches are not widely used.

The count-based SPECT approach is simple enough that any nuclear medicine laboratory using SPECT should be able to implement the technique. Its major advantages over the planar methods are that attenuation correction and background subtraction are unnecessary. The count per milliliter of blood is determined from blood in the center of the LV, so it has the same attenuation, on the average, and is counted with the same efficiency as the rest of the left ventricle. Background correction is unnecessary because there are no overlapping structures.

The only significant problem that remains is identification of the edge of the left ventricle, particularly the

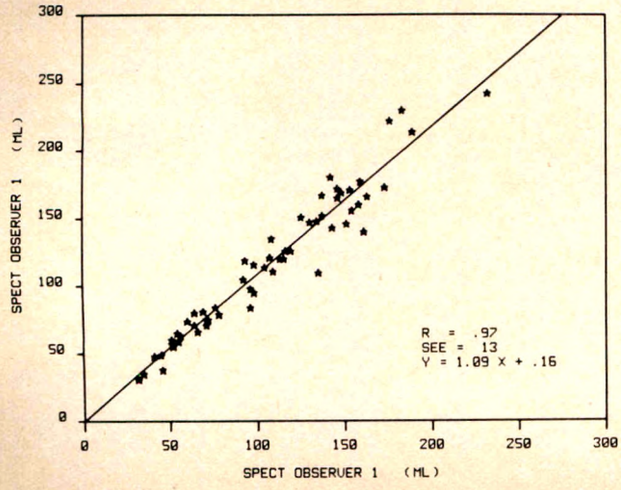

FIGURE 7. Comparison of separate determinations of left ventricular end-diastolic and end-systolic volumes by the same observer. SPECT = single-photon emission computed tomography.

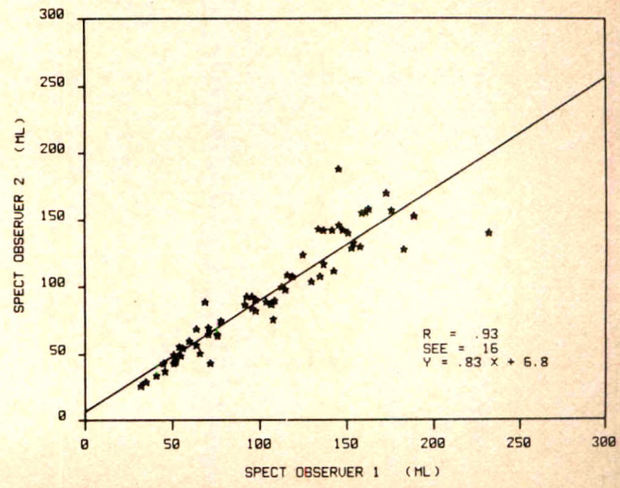

FIGURE 8. Comparison of determinations of left ventricular end-diastolic and end-systolic volumes by 2 observers. SPECT = single-photon emission computed tomography.

location of the mitral valve plane. Although it would probably be easier to identify the mitral valve plane using gated tomographic acquisition, we decided that the greater number of counts available in an ungated study would provide superior images, which should offset the advantages of the gated study. Our results are similar to those of Bunker et al,[38] who recently reported a similar technique using gated SPECT.

This emission tomographic method for LV volume measurement should apply equally well to the measurement of right ventricular volume and deserves further study. It may be possible to determine biventricular emission tomographic stroke volumes, which would allow quantitation of left-to-right shunt flow and valvular regurgitant flow.

We conclude that use of SPECT for measurement of LV volume is simple, accurate and reproducible and may be useful for diagnosis and management of cardiovascular disease.

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Echocardiographic Detection of Complete and Partial Papillary Muscle Rupture During Acute Myocardial Infarction

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Papillary muscle rupture produces severe mitral regurgitation, which is generally rapidly fatal. Because echocardiography can visualize the papillary muscles and mitral leaflets, it may detect papillary muscle rupture, prompting aggressive medical and surgical therapy. In 4 patients presenting to our hospital in 1983 and 1984, emergency echocardiography was instrumental in diagnosing either complete or partial papillary muscle rupture. Characteristics of the patient population are listed in Table I and pertinent echocardiographic features are illustrated in Figures 1 to 6.

In our 4 patients, echocardiography played a pivotal role in diagnosis and therapy. In the first patient, with complete papillary muscle rupture, there was no audible precordial murmur, and the initial pulmonary artery wedge pressure tracing inexplicably failed to reveal large "v" waves. In the second patient, mitral regurgitation was audible, but the patient improved markedly with vasodilator therapy. Emergency surgery was performed because of the echocardiographic diagnosis of partial papillary muscle rupture. Severe mitral regurgitation had not been suspected before echocardiography in the third patient with partial rupture. In the fourth patient, the presence of a mechanical defect in the setting of preserved septal and anterior wall motion prompted surgery.

Our 4 patients illustrate the spectrum of echocardiographic abnormalities that may be found in patients with complete or partial papillary muscle rupture. Complete papillary muscle rupture may be characterized by 1 or more 2-dimensional findings: abnormal cut-off of 1 papillary muscle; a mobile mass attached to chordae and to the mitral valve, which could simulate a valvular tumor, thrombus or vegetation; and a pattern of mitral prolapse or of a flail mitral leaflet.[1–4] Partial papillary muscle rupture has been reported only once previously. Nishimura et al[5] described an echocardio-

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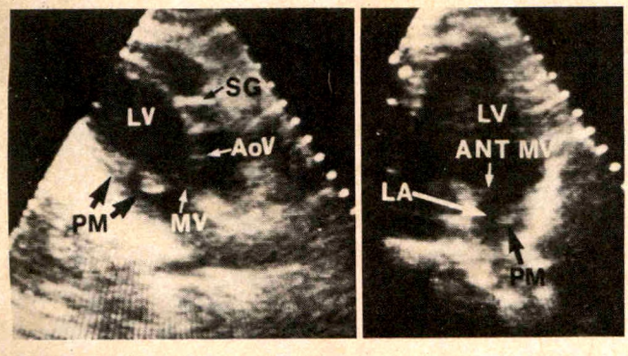

FIGURE 1. Long-axis diastolic (**left**) and apical systolic (**right**) images in the first patient, who had rupture of the posterior papillary muscle confirmed at surgery. In diastole, transection of 1 of the papillary muscles (PM) is seen. During systole, the PM is seen to flail into the left atrium (LA) (**right**). ANT MV = anterior mitral valve leaflet; AoV = aortic valve; LV = left ventricle; SG = Swan Ganz catheter in the right side of the heart.

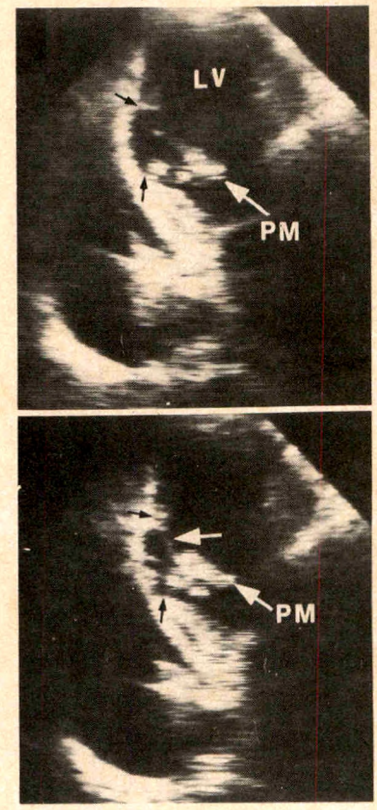

FIGURE 2. Apical views of the left ventricle (LV) obtained with slight changes in transducer angulation, from the second patient, in whom partial rupture of the posterior papillary muscle (PM) was confirmed at surgery. There is marked thinning of a localized portion of the inferoposterior wall (area between the 2 unlabeled **black arrows**). This region of myocardium was akinetic on the 2-dimensional scan. **Top,** no definite connection can be seen between the inferoposterior wall and the papillary muscle. With a slight change in transducer angulation, **(bottom),** however, a thread-like connection (**white arrow**) is evident, attaching the papillary muscle to the distal portion of the thinned myocardial region. There was increased echo-reflectivity from the papillary muscles, suggesting fibrosis.

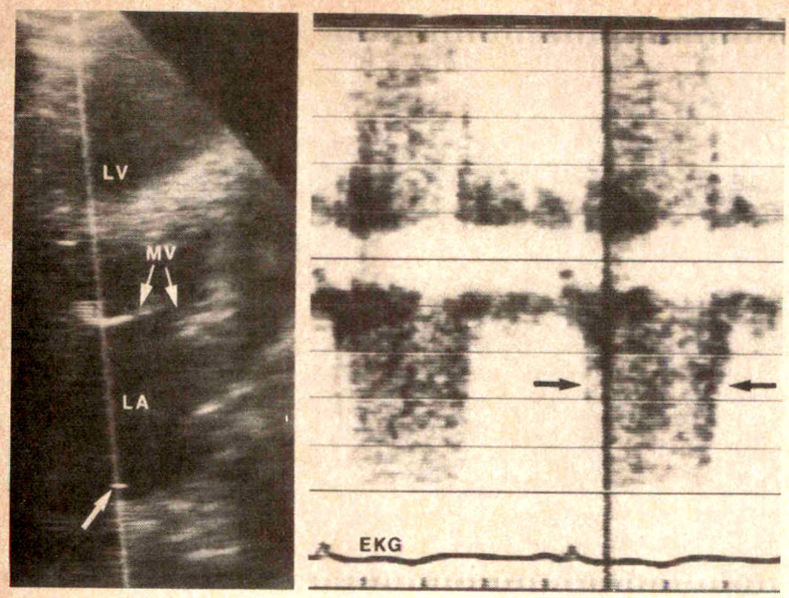

FIGURE 3. Apical 2-dimensional echocardiogram (**left**) and Doppler echocardiographic recording (**right**) from the second patient reveals holosystolic turbulence (**between 2 black arrows**) with sample volume placement (**unlabeled white arrow**) at the back wall of the left atrium (LA). EKG = electrocardiogram; LV = left ventricle; MV = mitral valve.

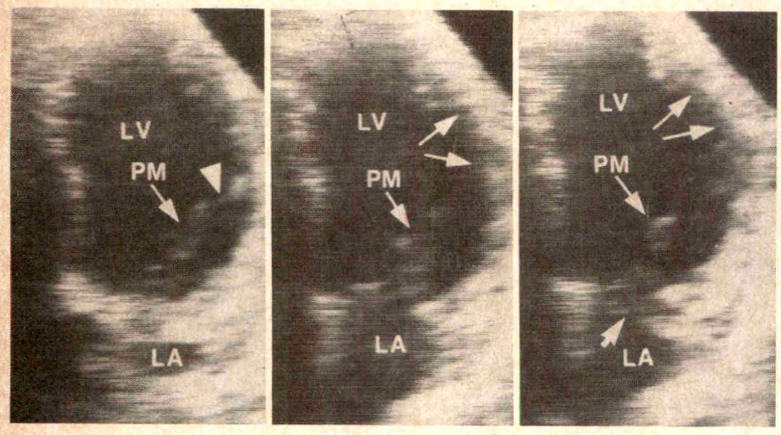

FIGURE 4. Apical views of the left ventricle (LV) in the third patient, with partial rupture of the posteromedial papillary muscle. **Left,** a tenuous attachment of the papillary muscle (PM) to the posterior wall is evident (**arrowhead**). **Middle** and **right,** dropout of myocardial echoes in the regions where PM attachment would be expected (**longer arrows**) and eliminate systolic protrusion of part of the PM into and through (**short arrow**) the mitral valve. LA = left artium.

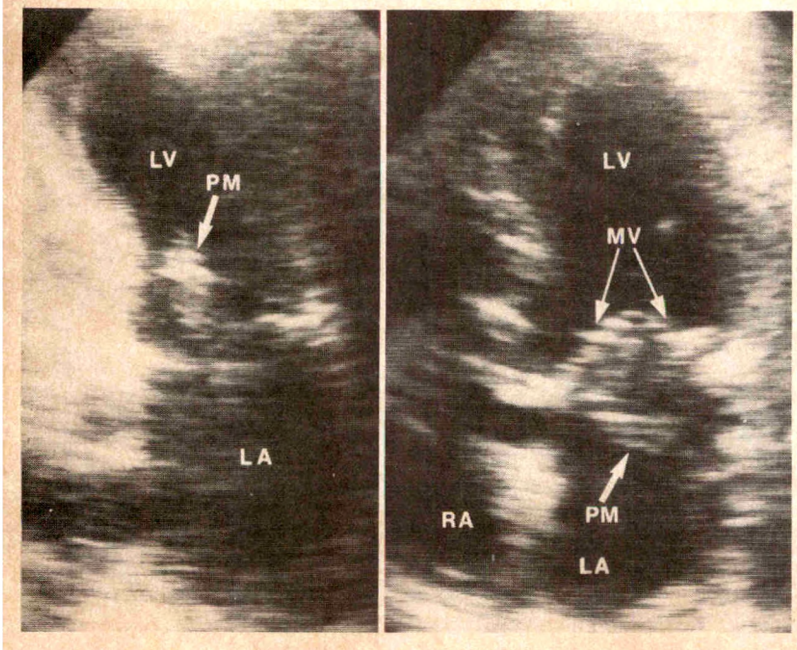

FIGURE 5. Apical views of the left ventricle (LV) in the fourth patient, with complete papillary muscle (PM) rupture. In diastole (**left**), the PM was seen to fling freely within the LV. In systole (**right**), the PM was thrust into the left atrium (LA). The flail motion of the anterior mitral valve (MV) leaflet is not evident in this view. RA = right atrium.

TABLE I Characteristics of the Patients

Pt	Age (yr) & Sex	Location AMI	Interval (days) from Onset of AMI to Clinical Deterioration	APE	SAP (s/d) (mm Hg)	Precordial Murmur	Mean PAWP (mm Hg)	CO (l/min)	MVR	Died	PM Rupture	
											Partial	Complete
1	45F	. . .	<1	+	50/-	0	30	2	+	0	0	+
2	82F	Inferior	21	0	120/80	+(3/6)	26	2.9	+	0	+	0
3	67F	Inferior	5	+	60/-	+(2/6)	—	—	0	+	+	0
4	84M	Inferior	7	+	40/-	+(3/6)	*28	*4.2	+	+	0	+

* Measurements performed after institution of intraaortic balloon counterpulsation.
AMI = acute myocardial infarction; APE = acute pulmonary edema; CO = cardiac output; MVR = mitral valve replacement; PAWP = pulmonary artery wedge pressure; PM = papillary muscle; SAP (s/d) = systemic arterial pressure (systolic/diastolic).

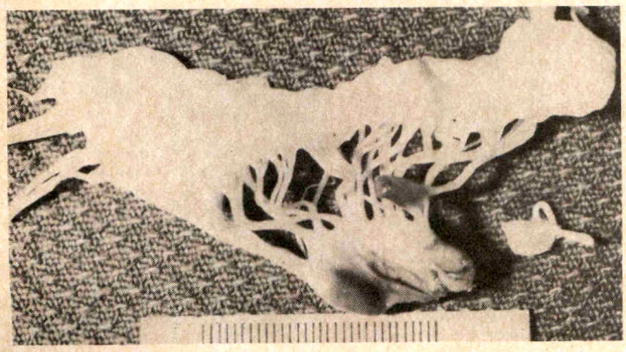

FIGURE 6. Operative specimen from the fourth patient illustrates the necrotic, jagged edge of the completely ruptured papillary muscle.

graphic pattern suggestive of disruption of part of the posteromedial papillary muscle in a patient whose condition subsequently deteriorated further; the patient was found to have complete papillary muscle rupture at unsuccessful mitral valve replacement.[5] Their report suggested that partial muscle rupture might be recognizable before complete rupture. By facilitating recognition of complete or partial papillary muscle rupture, echocardiography may prompt earlier surgical intervention.

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Sequential Balloon Technique in Angioplasty of Severe Coronary Arterial Obstructions

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Experienced angiographers have noted that attempts at percutaneous transluminal coronary angioplasty (PTCA) for stenoses of greater than 90% luminal diameter are associated with higher rates of both technical failure and complications.[1] Technical failure usually results from inability to pass the balloon catheter through a tiny and irregular residual channel, even though the guide wire had crossed previously. The best chance of passing through such lesions is to use a balloon that, in the deflated state, presents the smallest possible impaction surface (a "low profile") to the stenosis as it is advanced over the guide wire. On the other hand, the best chance of achieving both primary and long-term patency in PTCA is through use of a relatively large (higher profile) balloon which, when fully inflated, slightly exceeds the diameter of nearby normal segments of the artery.[2,3] We describe the clinical results of a sequential balloon technique that accomplishes both of these conflicting goals in the same procedure.

PTCA was applied in 74 severely narrowed or totally occluded vessels (45 left anterior descending (LAD) arteries, 14 circumflex arteries, 10 right coronary arteries, 4 coronary bypass grafts and 1 left main coronary artery) after initial successful passage of the guide wire through the obstruction. In most cases, these guide wires were either very flexible, straight-tipped, 300-cm exchange wires (Advanced Cardiovascular Systems—ACS) or steerable wires with slightly curved tips (USCI). A 2.0-mm ACS balloon catheter was then passed over the wire through the lesion. Once the balloon was in proper position, 2 to 4 inflations were carried out at 120

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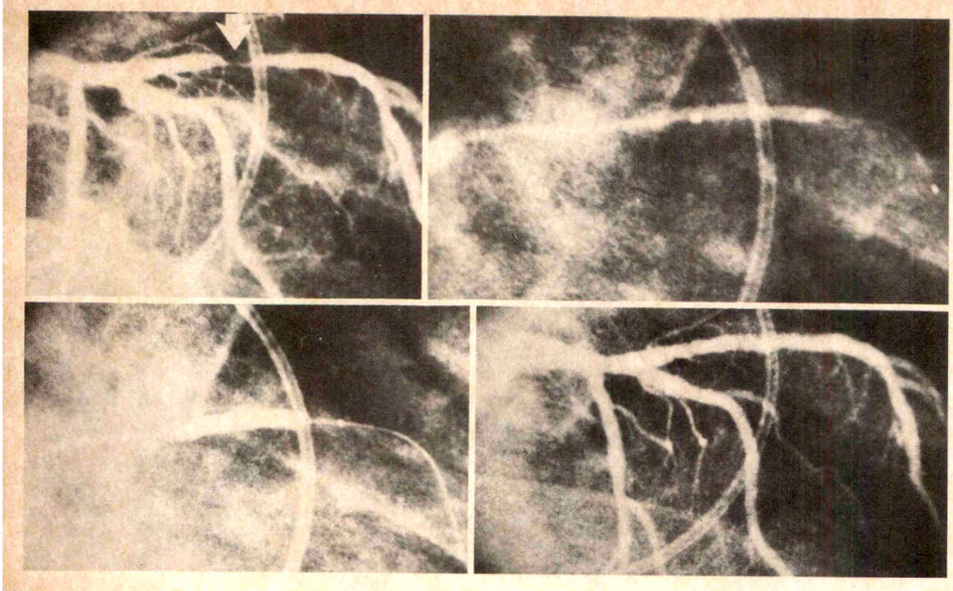

FIGURE 1. Right anterior oblique projections of left coronary arteriogram before, during and after percutaneous transluminal coronary angioplasty (PTCA) of the left anterior descending coronary artery. **A,** before PTCA there is severe stenosis of the proximal left anterior descending coronary artery (**arrow**). **B,** inflation of a 2.0-mm balloon. **C,** subsequent inflation of a 3.5-mm balloon after exchange over the guide wire. **D,** after PTCA, there is complete relief of the obstruction.

to 130 psi, each lasting approximately 45 seconds. If the steerable guide wire had been used initially, it was then removed and the 300-cm exchange wire was inserted through the balloon catheter (the tip of which was already beyond the stenosis) out into the distal segment of the vessel. The balloon was then retracted back into the guiding catheter, leaving the guide wire still positioned across the stenosis. A single contrast injection was obtained to check vessel patency. With the wire position carefully maintained under fluoroscopic control, the 2.0-mm balloon catheter was removed from the guiding catheter and a 3.0 or 3.5 mm ACS balloon catheter (depending on the size of the vessel) was inserted over the wire in its place. When this balloon was properly positioned, it also was inflated 2 to 4 times at 120 to 130 psi for 45 seconds each. The procedure was considered successful if the percent diameter stenosis was reduced by at least 20% and the residual stenosis at the end of the procedure did not exceed 60%.

Among the 74 vessels in which the sequential balloon technique was used, primary success was achieved in 65 (88%). These 65 successful PTCAs resulted in reduction of mean diameter stenosis from 92% to 28%. Of the 65 obstructions, 55 were initially at least 90% narrowed. Figure 1 is an example of application of the sequential balloon technique in PTCA of a severe LAD stenosis. Figure 2 shows its use in total occlusion of the distal right coronary artery. Among the 9 technical failures, 5 were a result of inability to cross the lesion with a 2.0-mm balloon after it had been satisfactorily crossed with a guide wire. In 1 additional failure, the lesion was initially dilated with a 2.0 mm balloon, but subsequently we could not cross it using a 3.5 mm balloon. In the last 3 cases, the lesions were crossed and dilated with both small and large balloons, but thrombi developed in the coronary arteries at the site of PTCA during the procedure.

Significant complications occurred in 4 cases (5%). The first 3 were the aforementioned thrombotic episodes during the procedure. Two of these 3 patients underwent successful emergency coronary bypass surgery (among the entire group, therefore, emergency bypass surgery was needed in 3%); the third had a small and uncomplicated anterior wall acute myocardial infarction. The fourth complication resulted from acute thrombosis of the LAD 5 days after initially successful PTCA. This patient was returned to the catheterization laboratory and underwent successful thrombolysis with intracoronary streptokinase.

The usefulness of the sequential balloon technique was suggested early in our PTCA experience. In several cases in which we wished to use 3.0- or 3.5-mm balloons to achieve complete dilatation, we could not initially pass these larger balloons over the guide wire through severe stenoses. In each instance, switching to a smaller, lower profile balloon resulted in successful passage. Creation of a track by first dilating with the small balloon then allowed subsequent introduction of the larger balloon without difficulty. The recent policy in our laboratory has been to routinely use the small balloons first in all patients with severe coronary obstructions, without even trying to initially pass the larger balloons.

Our experience shows that once a severe obstruction has been crossed with the guide wire, a 2.0-mm balloon can usually be passed (69 of 74 cases, 93%). When this small balloon is inflated initially to create a track, a larger balloon can almost always be passed across the lesion (68 of 69 cases, 99%). Thus, 2 goals are accomplished: initial crossing of the obstruction in a manner that is least traumatic and most likely to be successful, and subsequent use of a large balloon to create a wide residual lumen. Recent studies have emphasized the importance of the latter goal. Duprat et al[2] showed that residual stenoses after PTCA were minimized when the ratio of inflated balloon diameter to coronary arterial diameter was 1.1 to 1.3. Schmitz et al[3] performed follow-up coronary angiography in 86 patients a mean of 5.6 months after PTCA and found that in cases in which the balloon size had been smaller than the prestenotic vessel lumen, restenosis occurred in 36%, whereas it occurred in only 5% of cases in which the balloon size had exceeded the prestenotic vessel lumen.

This technique has several disadvantages. Procedure time is lengthened and intracoronary manipulation is

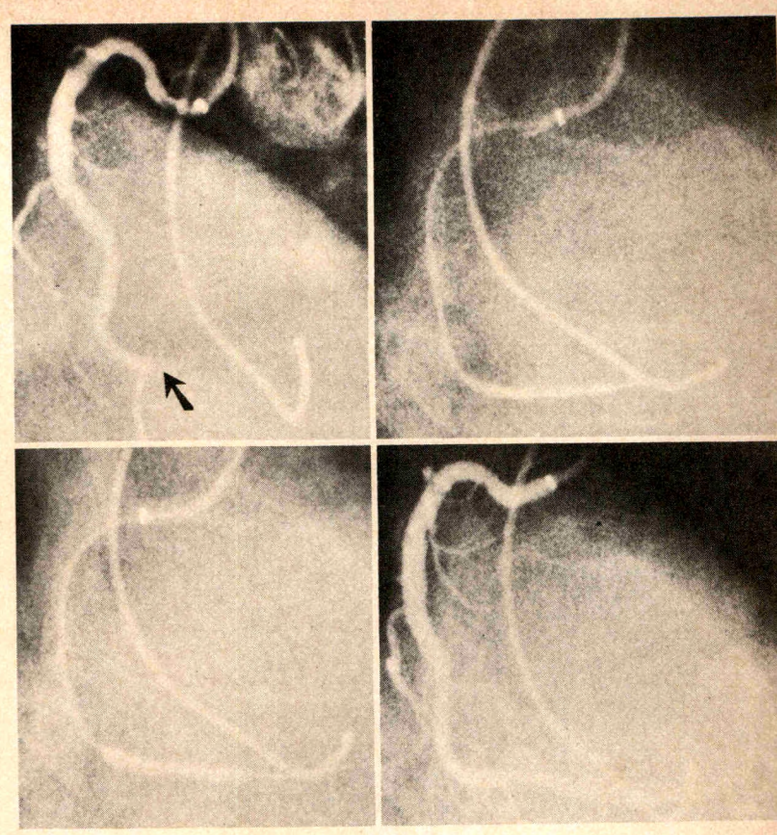

FIGURE 2. Left anterior oblique projections of right coronary arteriogram before, during and after percutaneous transluminal coronary angioplasty (PTCA) for complete obstruction of the distal right coronary artery (RCA). **A,** complete obstruction of the distal RCA (**arrow**) proximal to the origins of the posterior descending and the posterior left ventricular branches. **B,** after crossing the obstruction with a guide wire, a 2.0-mm balloon catheter was inserted and the balloon inflated. **C,** subsequent inflation of a 3.0-mm balloon, after catheter exchange over the guide wire. **D,** after PTCA, the obstruction has been almost completely relieved and normal anterograde flow restored to this strongly dominant RCA.

increased. Occasionally, displacement of the guide wire out of the coronary artery may inadvertently occur during balloon catheter exchange. Finally, the cost of the procedure is greater, because 2 balloon catheters are needed, and each costs $350 or more.

An early report by Cowley et al[4] in 1981 suggested that results of PTCA in vessels with stenoses of at least 90% are considerably worse than in less severely narrowed vessels. Our results, achieved with more modern equipment and techniques, show that even when severe narrowing or total occlusion is present, if a guide wire can be passed through the lesion, the likelihood of success approaches 90% and the incidence of complications is low. The sequential balloon technique appears to offer the best chance of traversing very severe obstructions and creating the widest possible residual lumen by 2 graded dilatations.

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Surgical Treatment of Medically Refractory Variant Angina Pectoris: Segmental Coronary Resection with Aortocoronary Bypass and Plexectomy

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Prinzmetal, in 1959, described the syndrome of variant angina pectoris (VAP). He hypothesized that episodes of ischemia were the result of a superimposed "normal increase in the tonus of the vessel wall."[1] The treatment of VAP consists of calcium channel blocking agents and nitrates. Although nitroglycerin is highly effective in the acute setting, the response to long-term nitrate administration is less satisfactory. Antman et al[2] reported that among patients in whom conventional therapy with nitrates and β-blocking agents fails, 87% had at least 50% reduction in anginal frequency with nifedipine. However, some patients are refractory to medical therapy. A variety of surgical procedures have been reported; their relative benefits remain controversial, and theoretical objections have been raised. In this report, we describe a patient with medically refractory coronary vasospasm who underwent a unique surgical procedure.

A 60-year old man was admitted in May 1980 for investigation of VAP. During hospitalization, the frequency of angina at rest increased to daily occurrences. Cardiac catheterization revealed a normal dominant right coronary artery. The circumflex artery was large and narrowed by 20% of its diameter distal to the take-off of a first lateral branch (Fig. 1A). After 3 doses of ergonovine, 0.05 mg intravenously at 2-minute intervals, the coronary arteries were again visualized. An 80% diameter narrowing in the proximal circumflex artery was induced (Fig. 1B), accompanied by severe chest pain and ST elevation in inferior leads. Although medical treatment was administered (Fig. 2) the pain persisted. In August, he was hospitalized with angina (up to 10 episodes/day). Holter monitoring revealed symptomatic episodes of 2:1 atrioventricular block with a ventricular rate as low as 30 beats/min requiring a VVI transvenous pacemaker. In April 1982, still disabled by resting angina, he was readmitted and underwent cardiac catheterization during which he had spontaneous angina and ST elevation. An injection into the left coronary artery revealed complete occlusion of the circumflex artery (Fig. 3A). The right coronary artery was normal. After injection of 5 mg of phentolamine into the left coronary artery, the artery became patent (Fig. 3B).

On April 17, 1982, a 2-cm resection of the spastic segment with ligation of the upper segment and saphenous vein bypass to the distal posterior circumflex artery and plexectomy were performed. No further episodes of angina occurred until January 1985. Cardiac catheterization was performed again in August 1984. The point of excision of the circumflex artery was seen (Fig. 3C). The graft to the distal circumflex was patent (Fig. 3D). A total of 0.8 mg of ergonovine was injected and resulted in no abnormal response.

Review of previous reports indicates that coronary artery bypass grafting (CABG) may be performed with an outcome comparable to that obtained with classic angina pectoris[3] in patients with VAP and significant fixed coronary stenosis. The addition of plexectomy may reduce the frequency of recurrent angina without increased operative risk.[4] Our patient, with VAP and close to normal coronary arteriographic findings, was intractable to medical treatment, including nitrates, nifedipine, verapamil, diltiazem and amiodarone. Angina persisted at a rate of about 10 episodes/day. Angiographically, the spontaneous coronary vasospasm was localized in a proximal nondominant circumflex artery at the site of early atherosclerotic changes. The segment of the circumflex artery displayed excessive vasoconstrictor activity, both spontaneously and in response to ergonovine (Fig. 1B and 2A). Regardless of whether the primary pathogenic mechanism is α-adrenergic or on the basis of local vasoconstriction supersensitivity (triggering zone), resection of the involved arterial segment plus plexectomy resulted in cessation of spontaneous angina and ergonovine inducible vasospasm. A similar approach was probably used by Heupler et al,[5] who reported three patients who underwent resection of the right coronary artery with

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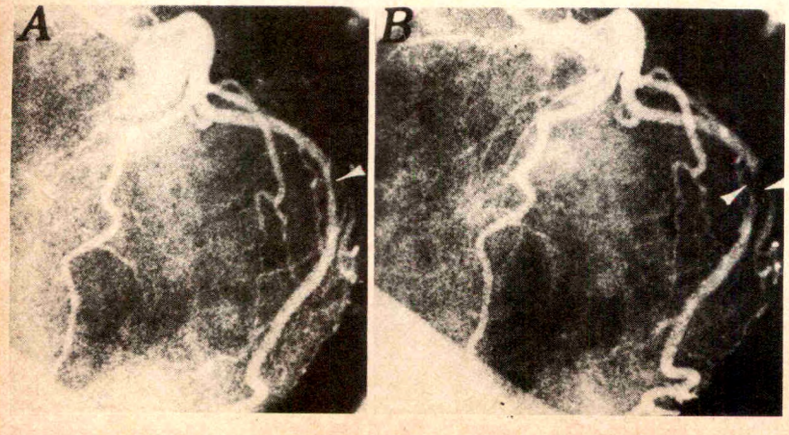

FIGURE 1. A, the left coronary artery had trifurcated into the left anterior descending, intermediate and circumflex branches. The circumflex artery had a 20% narrowing (**white arrow**). **B,** upon ergonovine challenge, an 80% focal spasm in the proximal circumflex artery was induced (**arrows**).

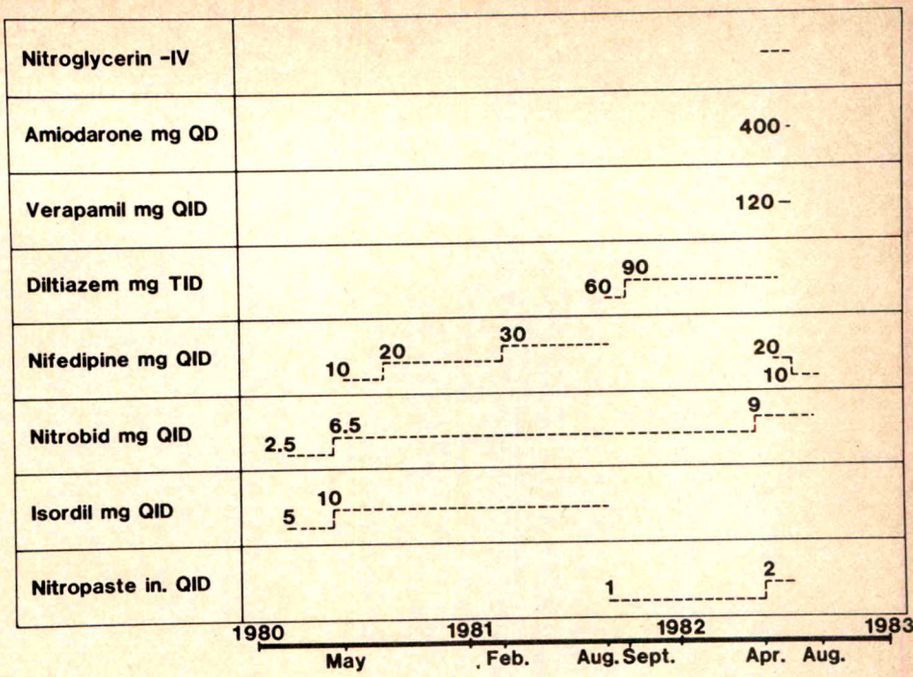

FIGURE 2. Pharmacologic interventions.

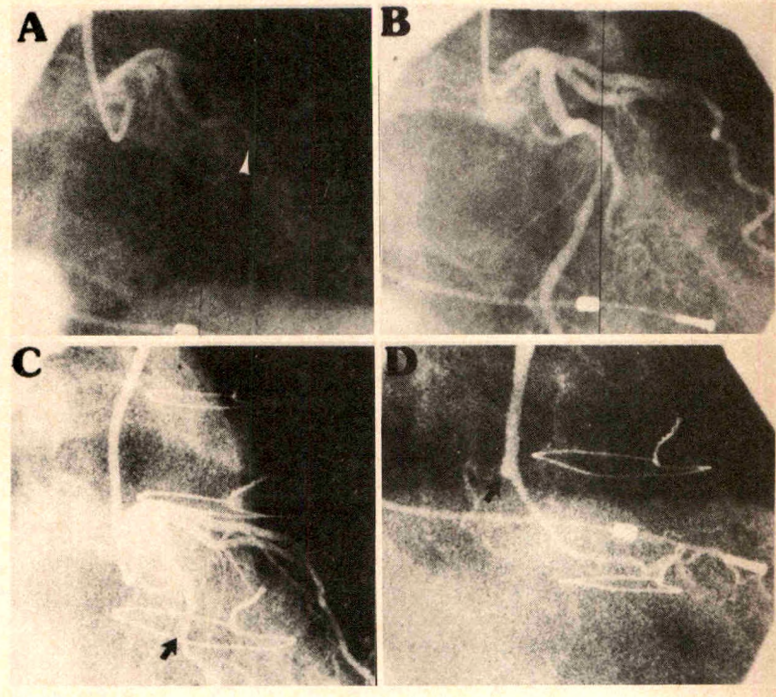

FIGURE 3. A, during repeat coronary angiography, spontaneous spasm with complete occlusion of the circumflex artery occurred in the region where ergonovine previously had induced spasm. **B,** after intracoronary administration of phentolamine, spasm disappeared. The patient underwent segmental resection of the circumflex artery in the area of angiographic spasm with vein bypass to the distal segment and plexectomy. **C,** Postoperatively, injection into the native left coronary artery shows a proximal stump occlusion (**arrow**) at the site of segmental resection of the circumflex artery. **D,** injection into the graft showed a patent distal circumflex artery.

CABG. Their detailed surgical and clinical courses were not provided.

Considering the variability of the course of VAP and the fact that spontaneous coronary spasm may be unpredictable, involving long segments of multiple vessels, this surgical approach might not be applicable to those patients without documentation of spontaneous or ergonovine-induced focal coronary vasospasm. We recommend combined coronary resection, CABG and plexectomy for patients with medically refractory VAP and focal coronary spasm. Randomized trials are unlikely, given the rarity of this entity.

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Relation of Acute Myocardial Infarction to Cocaine Abuse

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It is estimated that 10 million Americans have used cocaine and that 5 million use it regularly.[1] Although cocaine was first introduced in 1884 as a local anesthetic, little information appeared on the cardiovascular effects of cocaine use until recently. Cocaine abuse has been associated with tachycardia, systemic hypertension, ventricular arrhythmias, acute myocardial infarction (AMI) and sudden death.[2–7] Coleman et al[2] reported the first case of AMI associated with illicit use of cocaine; however, the patient was presumed to have underlying coronary artery disease, although he did not undergo coronary angiography. Kossowsky and Lyon[3] described 6 patients with AMI attributed to cocaine abuse. Four of their patients had some degree of atherosclerotic narrowing of the coronary arteries by angiography or autopsy and 2 did not have cardiac catheterization. Schachne et al[4] described another patient whose coronary arteries were normal. We describe another cocaine user who had AMI.

A 38-year-old white man had been well until age 32 years (April 1979), when he had a documented inferior wall AMI. After an uncomplicated course, he was transferred to the Bronx Veterans Administration Medical Center 3 weeks later. Blood pressure on admission was 120/80 mm Hg and serum cholesterol was normal. Cardiac catheterization and selective coronary angiography with left ventriculography was performed. The coronary arteries and the left ventricle were normal. Provocative maneuvers did not produce spasm. After discharge, he was asymptomatic but continued to use cocaine and heroin sporadically. Before AMI, he had increased his cocaine use to 3 times per week. He was readmitted to the coronary care unit 6 months later (November 1979) with an extensive anterior lateral wall AMI. Chest pain occurred 45 minutes after intranasal administration of cocaine. Selective coronary angiography again showed normal coronary arteries. The left ventricular ejection fraction was 68%. The infarctions were believed to have been induced by coronary artery spasm, but this could not be demonstrated by repeat ergonovine administration. He has been followed up by the cardiology service for the past 6 years. He has not used drugs for the past 5 years, although he continues to smoke cigarettes heavily and is a heavy alcohol binge drinker. He has not had chest pain or other cardiovascular symptoms since his last AMI. His blood pressure is 130/80 mm Hg. Left ventricular function by gated blood pool scintigraphy in August 1984 showed an ejection fraction of 53%.

Our patient is similar to the case reported by Schachne et al.[4] He also shares a common feature with several of the patients described by Kossowsky and Lyon[3] in that he was a mixed-substance abuser. Cocaine is a potent vasoconstrictor. It constricts blood vessels and prevents its own absorption.[5] AMI in any young patient who does not have risk factors should raise the suspicion of the possibility of coronary spasm related to recreational cocaine use. The prognosis for a patient who survives the initial infarction and has good left ventricular function appears to be excellent if cocaine usage is discontinued.

Acknowledgment: We gratefully acknowledge the excellent secretarial services rendered by Bernice McKay.

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Coronary Arterial Findings After Accidental Death Immediately After Successful Percutaneous Transluminal Coronary Angioplasty

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The mechanism by which percutaneous transluminal coronary angioplasty (PTCA) achieves its results remains minimally documented. Plaque compression and redistribution was the initial postulate for the success of arterial dilatation in peripheral atherosclerotic disease. Subsequent animal and human cadaver experiments[1] and human postmortem examinations[2,3] suggest plaque splitting and disruption with stretching of the nonatherosclerotic arterial wall. We present the pathologic findings in a patient who died immediately after a technically successful PTCA after an inadvertent intracoronary injection of lidocaine.

A 65-year-old woman with a 6-year history of angina pectoris was admitted with prolonged ischemic chest pain. Anteroseptal ST-segment depression was present, but no Q waves developed despite a moderate increase in cardiac en-

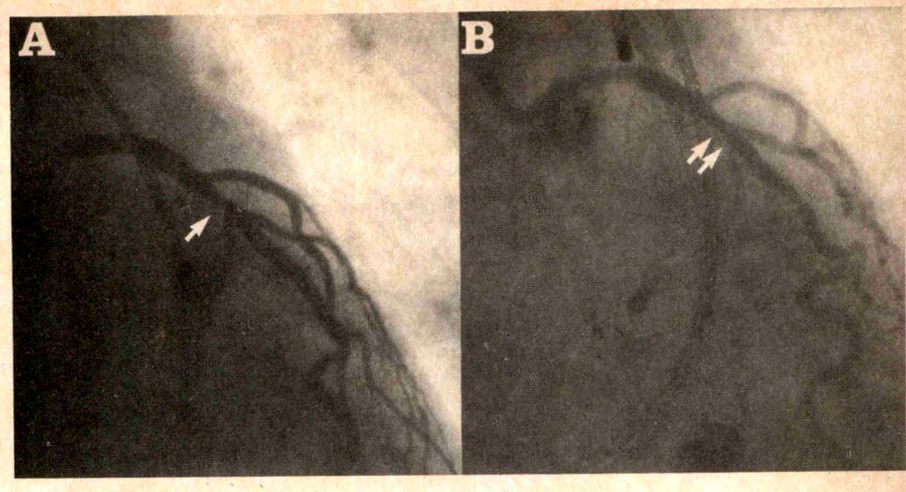

FIGURE 1. Left anterior descending coronary artery stenosis (**arrows**) (right anterior projection). **A,** before angioplasty; **B,** after angioplasty.

zyme levels. Cardiac catheterization after 10 days of continuing unstable angina revealed that the right coronary artery had an 85% narrowing of luminal diameter and the left circumflex artery was completely occluded. The left anterior descending artery (LAD) was narrowed 65% as seen in the right anterior oblique projection (Fig. 1A). The inferior left ventricular wall was moderately hypokinetic.

We decided to proceed to PTCA of the LAD and right coronary artery. PTCA of the LAD was accomplished using a 20–35 Meditech balloon and steerable guidewire system. Three dilatations to a maximal inflation pressure of 8 atm and total occlusion time of 135 seconds reduced the mean transstenotic gradient from 70 to 29 mm Hg. The postdilatation angiogram showed a reduction in diameter narrowing to 40% (Fig. 1B). In attempting a left anterior oblique view, 7 to 10 ml of a nonradiopaque fluid was injected into the left coronary artery. This had been mistaken for contrast medium and was later identified as 2% lidocaine. After 2 minutes of increased PR interval and QRS width, complete atrioventricular block developed, with no subsidiary escape rhythm. Resuscitative measures were unsuccessful.

Postmortem angiography confirmed a satisfactory angiographic result of PTCA. At autopsy an inferior infarct was found that was about the same age as the admission infarct. At the PTCA site, a split extended through the atheromatous plaque to the media with dissection and lifting of the plaque from the media (Fig. 2). A hemorrhagic area within the plaque opposite the split had an appearance that suggested that its occurrence predated PTCA.

In this patient, technically successful PTCA was achieved by splitting of the atheromatous plaque, and the patient died from an unrelated cause. Of the few previous reports of the pathologic findings in patients who died early after PTCA, plaque splitting was a frequent finding. However, most patients died from complications of acute myocardial infarction initiated by the PTCA.[2–4] Pathologic changes observed late after PTCA have been variable. An intense fibrocellular proliferation almost occluding the LAD lumen was found in 1 patient who died during repeat PTCA.[5]

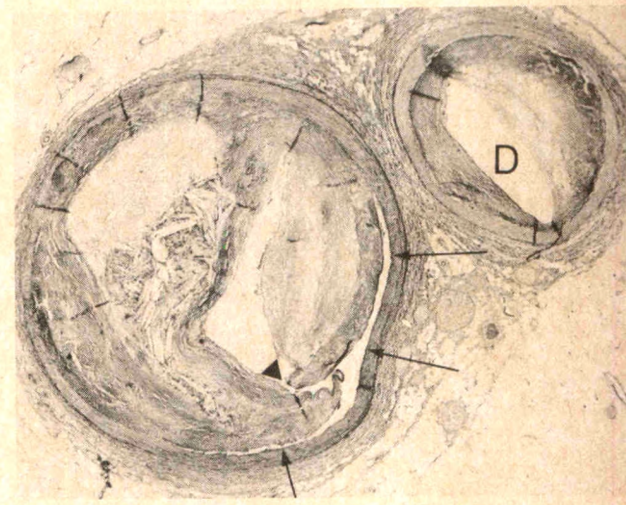

FIGURE 2. Cross section through the proximal part of the left anterior descending artery and adjacent diagonal branch (D). An atherosclerotic plaque with hemorrhage is narrowing the lumen. The plaque opposite shows disruption and splitting (**arrowhead**) and is dissected and lifted from the media (**arrows**). Apart from an atherosclerotic narrowing of the lumen, the diagonal branch does not show other changes.

Three other patients[4] showed no pathologic changes attributable to PTCA, although these were technically successful, and only 1 patient had recurrence of mild angina.

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Exercise-Related Bundle Branch Block in Children

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Exercise-related bundle branch block (BBB) in children is an uncommon occurrence. Most information about exercise-related BBB in children is anecdotal. We examined its frequency and significance among young persons with and without cardiac disease.

Maximal treadmill exercise testing was performed using the modified Bruce protocol[1] by 2,761 children and young adults, including 264 normal children, over a 10-year period (from July 1974 to August 1984). Electrocardiographic leads II, aVF and V_5 were continuously monitored throughout exercise with recording of a 1-lead electrocardiogram during each stage of exercise. Criteria for development of BBB were an abrupt QRS prolongation (longer than 0.12 second) during exercise and a narrow QRS at rest.

BBB developed during exercise testing in 2 girls and in 4 boys, aged 9 to 18 years (mean 11). None had a normal heart: 5 had congenital heart disease (valvular aortic stenosis (AS) in 1 patient, subvalvular AS in 2 patients, postoperative repair of primum atrial septal defect in 1, and postoperative repair of tetralogy of Fallot in 1) and 1 had cardiomyopathy (Table I). ST-segment depression (greater than 2 mm, flat or downgoing at 0.08 second) was found in 3 of the patients with exercise-induced BBB. A right BBB pattern was found in 4 patients and left BBB pattern in 2 (1 with cardiomyopathy and 1 with subaortic stenosis). Heart rate at onset ranged from 100 to 195 beats/min (mean 136). Rate at return to normal conduction ranged from 72 to 160 beats/min (mean 119). In each case, the rate at onset of BBB was higher than the rate at return to normal condition. No arrhythmias were observed during exercise testing in any patient. Physical working capacity was under the 5th percentile for age in the patient with cardiomyopathy. The patient with repaired atrial septal defect was active in sports. Each patient with valvular AS or subvalvular AS and the child with tetralogy of Fallot were normally active, but had been restricted from participation in competitive sports because of cardiac disease. The child with cardiomyopathy was limited in activity and had been restricted from sports competition. Follow-up studies ranged from 1 to 8 years (mean 4.2). No patient died during follow-up. One child required further surgery for AS. BBB during exercise was not observed in the 264 normal children.

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The incidence of exercise-related BBB in an adult population with heart disease is approximately 0.4 to 0.9%.[2] Our incidence of 0.2% indicates that exercise-related BBB is less frequent among children than among adults with heart-disease. This finding is consistent with the lower incidence of aberrant conduction with supraventricular tachycardia in children[3] than in adults.

BBB during exercise may be confused with ventricular tachycardia. Lack of atrioventricular dissociation and a rate similar to the narrow QRS rate at both the onset and recovery from bundle branch configuration allow this differentiation (Fig. 1 to 3).

Sandberg[4] believed that the development of BBB in an older population was related to ischemic cardiac disease, whereas exercise-related BBB in a younger population was unrelated to cardiac disease. Our observations on a young population indicate that exercise-related BBB is associated with cardiac disease.

Whereas exercise BBB is predominantly related to coronary disease among adults,[2,5] we noted an association with AS among children. The occurrence of exercise-related BBB was present in 3 of 153 of our patients with AS who underwent exercise testing. AS with rate-related BBB in adult patients was reported by Fisch et al.[2] Exercise BBB after repair of congenital cardiac disease was observed in subjects in our study; this finding has not been previously emphasized.

BBB that develops during exercise makes interpretation of ST segments difficult or impossible. Three of our patients had "ischemic" ST-segment changes before onset of BBB. Although exercise-related BBB could be related to autonomic causes[2] and may be unrelated to

TABLE I Clinical Data in Six Patients with Exercise-Related Bundle Branch Block (BBB)

Pt	Age (yr) & Sex	Diagnosis	Form of BBB	Onset HR (beats/min)	HR at Return to NL QRS (beats/min)	Peak HR (beats/min)	"Ischemic" ST Changes Before BBB	Physical Working Capacity (Percentile)
1	18M	Valvular AS	Right	190	160	205	+	>95th
2	10M	Subvalvular AS	Right	110	104	178	0	80th
3	12F	Subvalvular AS	Left	104	81	150	+	25th
4	4F	Primum ASD (PO)	Right	195	160	195	0	10th
5	13M	ToF (PO)	Right	170	140	197	0	90th
6	17M	IDC	Left	100	72	200	+	<5th

AS = aortic stenosis; ASD = atrial septal defect; HR = heart rate; IDC = idiopathic dilated cardiomyopathy; NL = normal; PO = postoperative; ToF = tetralogy of Fallot; + = present; 0 = not present.

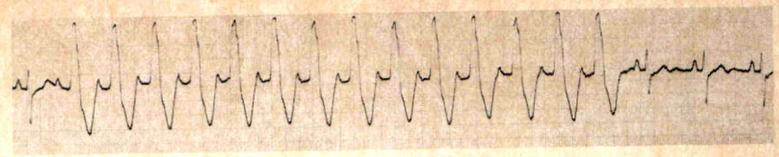

FIGURE 1. Exercise-related bundle branch block in lead II in a patient with cardiomyopathy. Note PR-interval prolongation with onset of bundle block, which may suggest abnormality of the atrioventricular node.

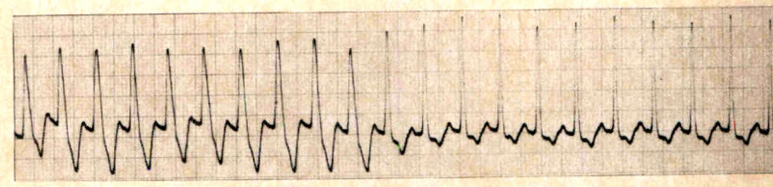

FIGURE 2. Exercise-related bundle branch block in lead V_5 in a patient with aortic stenosis. Termination of bundle branch block is observed in the postexercise recovery period.

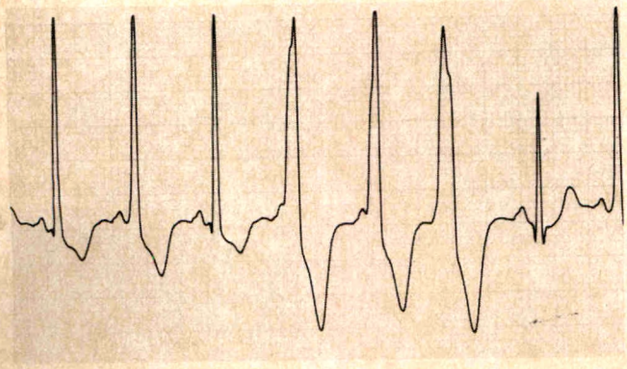

FIGURE 3. Exercise-related ventricular tachycardia. This is differentiated from exercise-related bundle branch block by the presence of atrioventricular dissociation.

ischemia in younger persons,[4,6] nuclear testing may be of value in further evaluation of the young patient in whom BBB develops during exercise.[7]

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Pacemaker Twiddler's Syndrome: An Important Cause of Diaphragmatic Pacing

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Pacemaker Twiddler's syndrome (PTS) is characterized by permanent pacemaker malfunction owing to pacemaker generator manipulation by the patient. The classic syndrome, as first described by Bayliss et al,[1] consists of failure of ventricular pacing and occurrence of diaphragmatic pacing due to phrenic nerve stimulation as a result of the manipulation of the prepectoral pulse generator by the patient. In that patient, the pacemaker lead was turned around the generator in the capacious packet by a "capstan effect." This syndrome is rare; only 3 patients have been described.[1,2] The syndrome has been broadened by some to include: any significant generator manipulation,[2] or a "flipped pulse generator" due to manipulation of abdominally implanted generator,[2,3] and an attempted suicide by generator manipulation.[4] We describe a patient with PTS to reemphasize the classic syndrome with its unusual clinical presentation.

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A 76-year-old man had recurrent near syncope associated with atrial fibrillation with ventricular response, from 38 to 50 beats/min, 7 years after uncomplicated aortic valve replacement with the Smeloff-Cutter prosthesis. A VVI transvenous permanent pacemaker was implanted in the left pectoral region. A tined ventricular lead was introduced through the left subclavian vein; placement of the lead in the right ventricular apex was confirmed by a chest radiograph (Fig. 1), and ventricular pacing thresholds were appropriate. One week later he returned to the emergency room with a heart rate of 40 to 60 beats/min with rhythmic jerking movements of the left upper abdomen at a rate of 70 beats/min. The implantation site was well healed. An electrocardiogram showed atrial fibrillation with a slow ventricular response. The pacemaker generator pulse artifacts were also seen on the electrocardiogram at rate of 70 beats/min, but there was failure to sense or pace the ventricle. Lead perforation was suspected. The chest radiograph, however, showed that the ventricular lead was wrapped repeatedly around the pulse generator; its distal lead tip was located near the first

rib (Fig. 2). The patient denied manipulating the pulse generator but mentioned frequent itching in the left axilla, which had led him to scratch it vigorously. Using an external programmer, the pacemaker voltage amplitude was halved and the pulse width was decreased. Immediately, the rhythmic movements of the left upper abdomen ceased. When the previous pacemaker settings were then temporarily restored, the jerking movements of the upper abdomen at the rate of 70 beats/min were again noted. Rhythmic arm twitching could not be elicited by compression in the supraclavicular fossa or change in the patient's position. Later, at the time of repositioning the ventricular lead, the pulse generator was again reprogrammed to its initial settings; however, it did not induce diaphragmatic contractions. A chest radiograph showed that the distal end of the ventricular lead was now positioned in the right atrium (Fig. 3). Once again, the patient denied having manipulated the pulse generator. During repositioning of the pacemaker lead, the pulse generator could be moved freely within the large generator pocket. A tined ventricular lead was reinserted, and the pulse generator was tied into a Dacron® pouch, which was then sutured to the prepectoral fascia in several places with nonabsorbable sutures. During a 5-month follow-up, he was free of recurrent problems with normal pacemaker function.

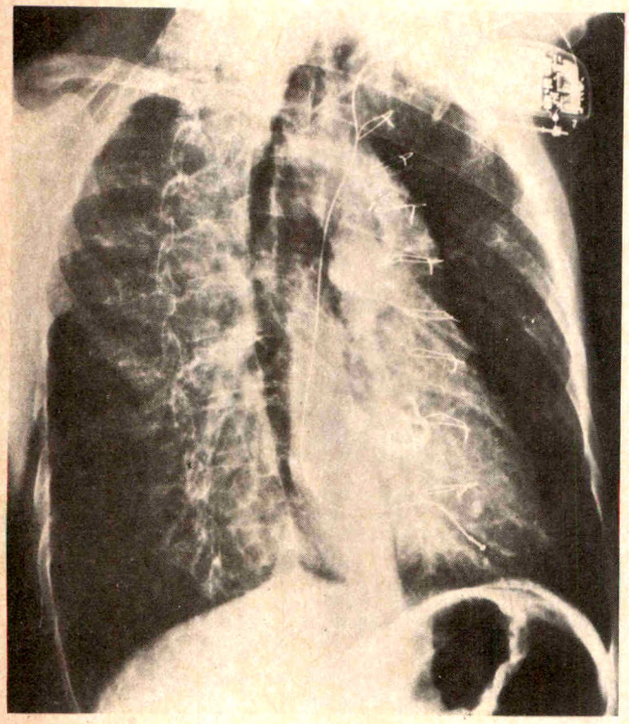

FIGURE 1. Chest radiograph (right anterior oblique position) after pacemaker implant showing tined lead at right ventricular apex.

Diaphragmatic pacing is usually associated with perforation of the right ventricle by the lead, but in our patient, as described in the classic syndrome, it was a result of ipsilateral phrenic nerve stimulation. The phrenic nerve enters the thorax by crossing from the lateral to the medial side, in front of the subclavin artery, and behind the subclavian vein just at the level of the clavicle.[5] This position corresponds to the electrode tip position seen on the chest radiograph. The pulse generator caused diaphragmatic pacing by phrenic nerve stimulation. This was confirmed in 2 ways: (1) When the lead tip was at the clavicle, changing the generator output controlled diaphragmatic pacing; and (2) after the patient manipulated the lead tip from the left subclavian vein to the right atrium, changing the

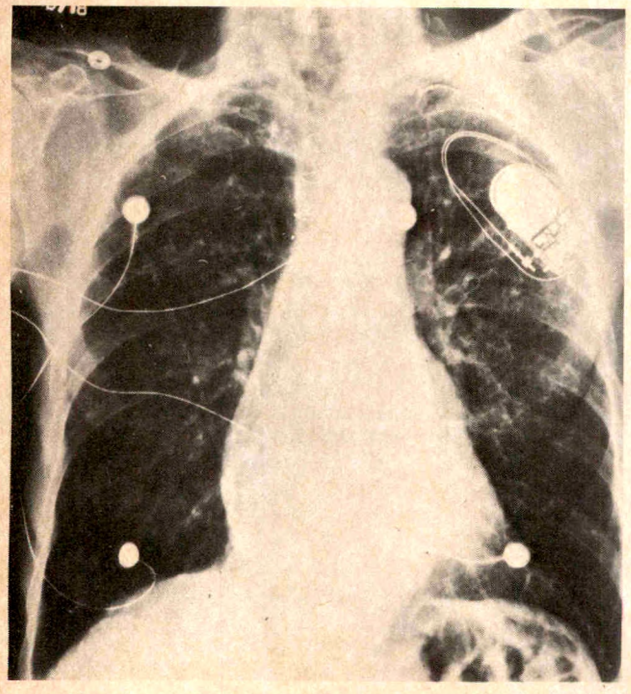

FIGURE 2. Chest radiograph on readmission during left diaphragmatic pacing. The lead tip is at the head of the first rib and the clavicle, where the phrenic nerve usually enters the thorax. The lead is wound around the pacer box by a "capstan effect."

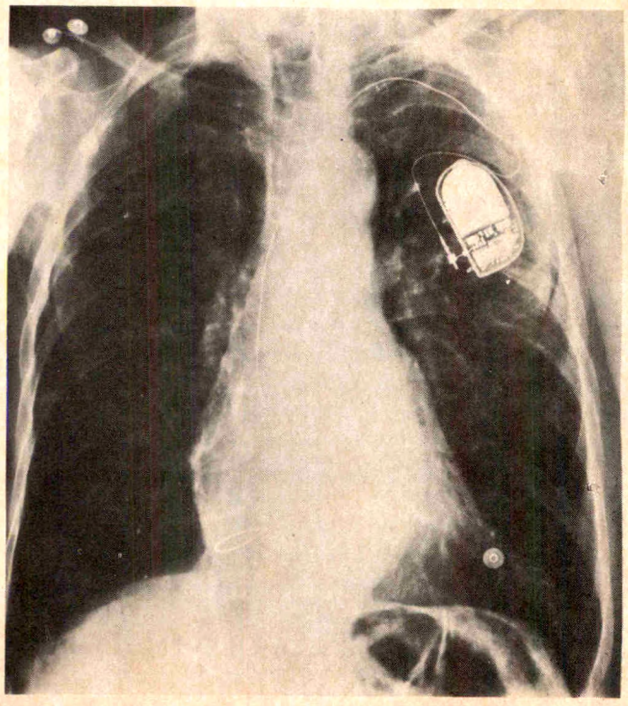

FIGURE 3. Chest radiograph just before reimplantation showing that the lead tip is now in the right atrium.

generator output failed to cause diaphragmatic pacing. With the use of tined leads, early lead dislodgement is infrequent (2 of 602 leads).[6] Lead dislodgement into the superior vena cava or the innominate vein with loss of pacer function and direct pacing of the phrenic nerve has not been previously reported with tined leads.

We believe that the broadened general use of the term PTS has obscured the original clinical syndrome with its interesting findings. Classic PTS and lead perforation should be considered when evaluating patients with pacemakers and diaphragmatic pacing.

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Arrhythmogenic Right Ventricular Dysplasia in a Family

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Arrhythmogenic right ventricular dysplasia (ARVD) is an uncommon cardiomyopathy affecting primarily the right ventricle in which ventricular tachycardia of a left bundle branch block (LBBB) configuration is frequently the presenting finding.[1] We describe a family with a high incidence of ARVD documented by echocardiography or histologic examination of the heart.

Case 1: *A 21-year-old woman, the oldest of 5 siblings, was in apparent excellent health before dying suddenly while playing softball (Fig. 1). At autopsy, a markedly dilated and thin-walled right ventricle and a normal left ventricle were found. Histologic examination revealed prominent replacement of the myocardium with connective tissue.*

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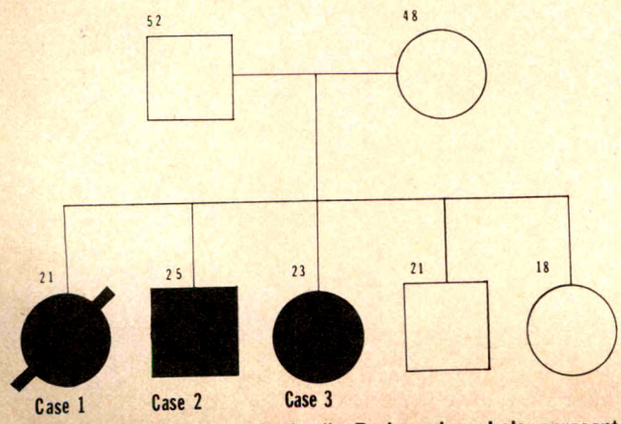

FIGURE 1. The pedigree of the family. **Darkened symbols** represent an affected member. Ages are given above the symbol.

Case 2: *A 25-year-old man had palpitations and presyncope while exercising. Results of physical examination were normal. A 24-hour electrocardiogram revealed nonsustained, monomorphic ventricular tachycardia with LBBB configuration at a cycle length of 420 ms. Electrocardiographic findings were normal except for an rSr′ pattern in lead V_1 and inverted T waves inferiorly and in leads V_1 to V_6. Chest radiograph showed a mild increase in heart size. Both echocardiography and radionuclide ventriculography showed a dilated, hypocontractile right ventricle with a normal left ventricle at rest.*

During electrophysiologic testing, sustained ventricular tachycardia identical to the clinical tachycardia was induced with programmed ventricular stimulation (Fig. 2). Sotalol therapy was effective in preventing tachycardia induction. A percutaneous ventricular biopsy specimen revealed extensive replacement of myocardium by fibrous tissue, confirming the diagnosis of ARVD. Immunochemical analysis of the specimen was normal. The patient is doing well with sotalol treatment at 6 months of follow-up.

Case 3: *A 23-year-old woman complained of short episodes of palpitations for the past 3 years. Results of physical examination were normal. Seventy-two-hour Holter monitoring showed several 3-beat salvos of ventricular tachycardia of LBBB configuration. T waves were inverted inferiorly and in leads V_1 to V_6. Chest radiograph was normal. Both echocardiography and radionuclide ventriculography showed right ventricular dilatation and hypocontractility with a*

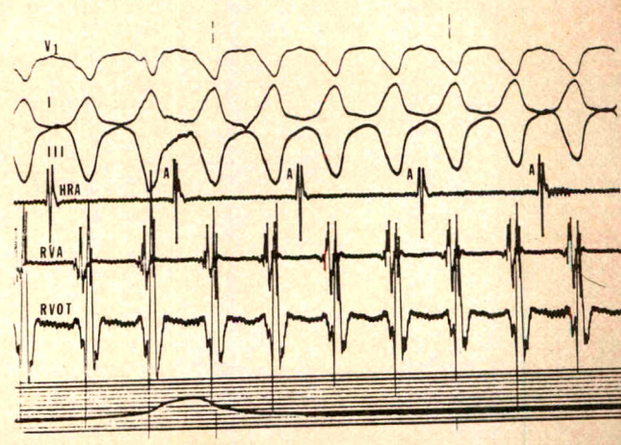

FIGURE 2. Ventricular tachycardia in Case 2. **Top** to **bottom,** leads V_1, I and III, and intracardiac electrograms from the high right atrium (HRA), right ventricular apex (RVA) and right ventricular outflow tract (RVOT). The ventricular tachycardia has left bundle branch block pattern and a superior axis.

normal left ventricle. Ventricular tachycardia was not inducible during electrophysiologic testing. She continues to do well without antiarrhythmic therapy.

Family studies: *All other family members are asymptomatic and electrocardiograms and echocardiograms recorded for the remaining 2 siblings and both parents are normal.*

There have been several reports of ventricular tachycardia of LBBB configuration or of sudden deaths in relatives of patients with ARVD.[1–4] Although this is suggestive of a familial occurrence of ARVD, definitive evidence of organic disease of the right ventricle in these relatives was not obtained. Uhl's anomaly, which probably represents a more severe manifestation of ARVD, has been observed in family clusters.[5–7] The high incidence of affected siblings in the family described here (3 of 5) would appear to make a genetic pattern of autosomal recessive unlikely. A pattern of autosomal dominance with incomplete penetrance would appear to be more likely. Alternatively, familial exposure to a common toxic or infectious agent, perhaps with a genetic predisposition, is another possibility.

In view of the evidence presented that ARVD may be familial, we recommend that electrocardiograms and echocardiograms be obtained in family members. The role of antiarrhythmic prophylaxis for asymptomatic affected family members is not known.

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Induction and Termination of Ventricular Tachycardia by Changing Body Posture

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In a limited number of cases, the initiation of ventricular tachycardia (VT) is related to body posture.[1] In this report, we describe a patient with VT that was initiated by assuming a supine position and terminated by standing.

A 27-year-old man presented with episodes of recurrent VT for 3 years. Physical examination and cardiac catheterization disclosed no significant abnormalities. An intracardiac electrogram during the tachycardia confirmed VT, and its origin was at the mid-inferior left ventricular wall (Fig. 1). Continuous monitoring repeatedly showed that VT occurred whenever he was recumbent. It lasted for 1 to 2 minutes when he stayed in a supine position, but was always terminated by standing (Fig. 2). The VT was terminated during a phase 2 Valsalva maneuver and resumed during a phase 4 Valsalva maneuver (Fig. 3). Intravenous (i.v.) injection of phenylephrine (0.2 mg) and volume loading with fluids induced VT. Pretreatment with i.v. atropine (1.0 mg) did not alter the characteristics of the initiation and termination of VT. Treadmill exercise testing and isoproterenol infusion (to 0.4 μg/min) failed to induce VT. There was no relation between heart rate and the occurrence of VT during these maneuvers. The echocardiogram verified that the initiation and termination of VT were closely related to left ventricular (LV) size. Figure 4 shows that LV size decreased during phase 2 Valsalva maneuver, at which time VT was terminated, while LV size increased during phase 4 Valsalva maneuver, at which time VT was initiated. Programmed ventricular stimulation did not induce VT nor terminate it, suggesting that the mechanism of VT was automaticity.

Characteristically, VT in our patient was initiated by assuming a supine position, by i.v. phenylephrine, by volume loading with fluids, and during a phase 4 Valsalva maneuver; it was terminated by standing and during a phase 2 Valsalva maneuver. Peters et al[1] described a case of VT that occurred only when the patient was in an upright position and always terminated when

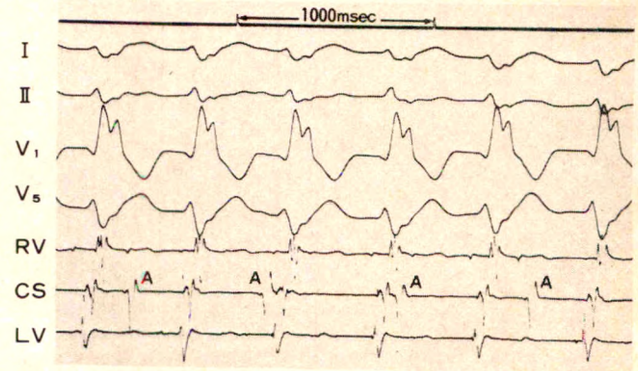

FIGURE 1. Simultaneous recordings of surface electrocardiograms in leads I, II, V_1 and V_5 and intracardiac electrograms during tachycardia. Atrioventricular dissociation is present during tachycardia. A = atrial activity; CS = coronary sinus; LV = left ventricular midinferior region; RV = right ventricular apex.

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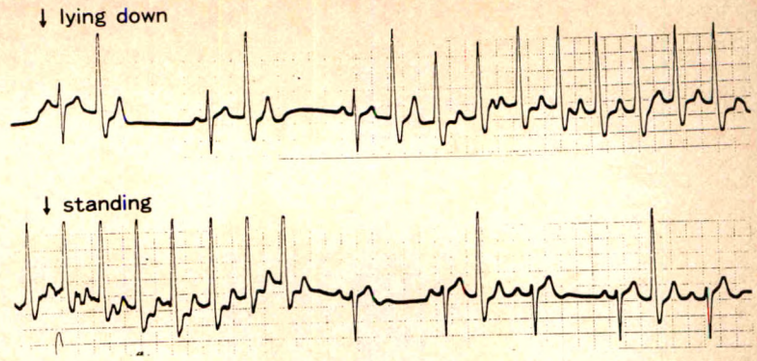

FIGURE 2. Continuous electrocardiographic monitoring showing that tachycardia is initiated by lying down and terminated by standing.

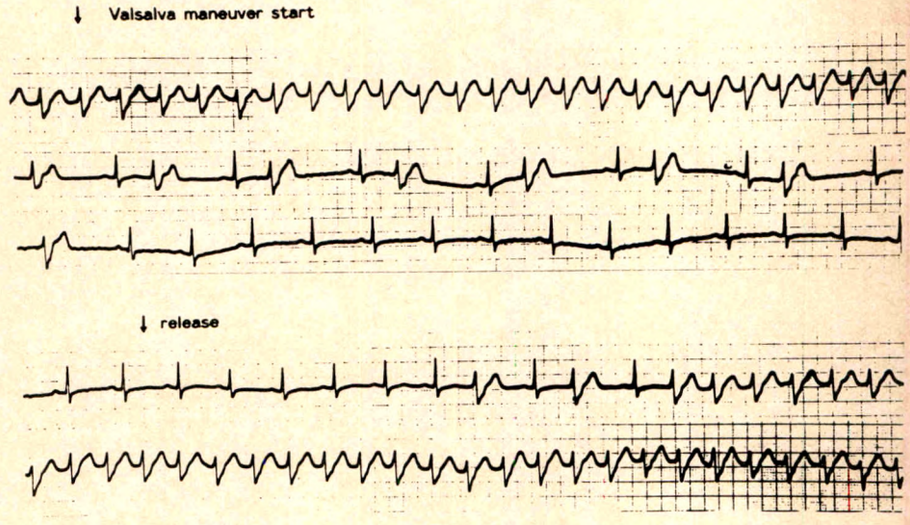

FIGURE 3. Continuous electrocardiographic monitoring during a Valsalva maneuver. Note that ventricular tachycardia is terminated during phase 2, and initiated during the phase 4 Valsalva maneuver.

the patient was lying down. They postulated that the attacks of VT were due to unusually strong sympathetic tone produced by assuming an upright position. In contrast, VT in the present patient was initiated by assuming a supine position and always terminated by standing. Some VTs were reported to have terminated by vagal stimuli.[2] Usually, the most effective vagal stimulation regarding termination of VT is produced by i.v. phenylephrine. In this patient VT was initiated, instead of terminated, by phenylephrine. Also, pretreatment with atropine did not alter the characteristics of the initiation and termination of VT. These findings suggest that neither sympathetic nor vagal stimuli plays an important role in the initiation and termination of VT in this patient. Change in heart rate is mechanism of induction of some VT. In this patient, VT was initiated not only during a phase 4 Valsalva maneuver when his heart rate increased, but also by phenylephrine injection when it decreased. A supine position, i.v. phenylephrine, volume loading with fluids, and phase 4 of the Valsalva maneuver—all of which induced VT in the present patient—increase LV size.[3,4] This was confirmed by measuring LV size with echocardiography during a Valsalva maneuver. Thus, it is possible that an increase in LV size was responsible for the occurrence

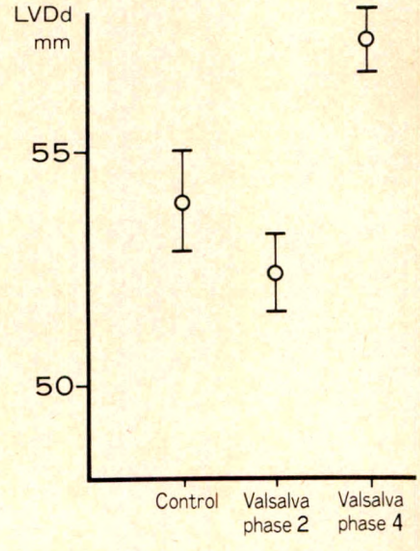

FIGURE 4. The change of end-diastolic dimension of the left ventricle (LVDd) during the Valsalva maneuver estimated echocardiographically. Note that LVDd decreases during phase 2, at which time the ventricular tachycardia is terminated, while the LVDd increases during phase 4, at which time the ventricular tachycardia is initiated. **Bars,** standard error of the mean.

of VT in this case. Recently, Waxman et al[3] reported 9 patients with VT that could be terminated by a Valsalva maneuver. They postulated that the termination was due to an abrupt reduction of cardiac size. The VT in this patient is unique in that not only the termination, but also the initiation of the VT were closely related to LV size.

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Norepinephrine Infusions in Congestive Heart Failure

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Norepinephrine (NE) levels are frequently increased in patients with congestive heart failure (CHF).[1,2] The significance of high circulating NE levels in patients with CHF is unknown. To provide data concerning the effects of an increase in plasma NE on hemodynamic function and plasma renin activity in CHF, we measured these variables in response to an infusion of exogenous NE in a group of 8 patients with CHF. Overall, the results do not suggest an important effect of circulating NE on either hemodynamic variables or plasma renin activity in CHF.

Eight patients participated in these studies. All patients had chronic CHF (New York Heart Association Functional Class II or III) of at least several months' duration but were in clinically stable condition at the time of study. Four had primary and 4 had ischemic cardiomyopathy. All had enlarged hearts on chest radiograph and decreased ejection fractions by either radionuclide scanning or echocardiography. All were receiving digitalis and diuretic therapy and some were taking vasodilators. None was taking α_1-blocking agents. All medications other than antiarrhythmic drugs were withheld on the day of study.

After all patients gave informed consent, hemodynamic monitoring was instituted with the patient in the postabsorptive state. After at least 30 minutes of rest following placement of Swan-Ganz and arterial catheters, baseline hemodynamic measurements were made and repeated 15 minutes later. If these values were within 10% of one another they were accepted as basal, with averaged values used as control measurements. Blood was then drawn from the arterial catheter for determination of plasma NE and renin activity. An infusion of Levophed® (L-NE) was then begun into a peripheral vein at 0.1 μg/min and subsequently increased to 0.5 μg/min, and then to 1.0, 1.5 and 2.5 μg/min. Each infusion rate was maintained for 20 minutes, with hemodynamic measurements made between the 10th and 20th minute of each stage, and blood resampled for NE and renin just before increasing to the next level. At the conclusion of the 2.5-μg/min infusion, blood was sampled a final time and the study concluded.

Plasma for NE analysis was separated immediately by cold centrifugation, frozen and stored at −20°F for later analysis by radioenzymatic assay[3]; in our laboratory this has an inter- and intraassay coefficient of variation under 8%. Plasma renin activity was measured by radioimmunoassay[4] with similar reliability in our laboratory.

All data were analyzed using analysis of variance for repeated measures on the same elements.

Baseline hemodynamic variables in those patients with CHF included a heart rate of 79 ± 8.5 beats/min, mean arterial pressure of 79 ± 10 mm Hg, cardiac index of 2.5 ± 0.56 liter/min/m^2 and systemic vascular resistance of 1,272 ± 311 dynes cm^{-5}. Right atrial pressure was 12 ± 7 mm Hg and left ventricular filling pressure, estimate from either one pulmonary capillary wedge or pulmonary artery diastolic pressure, was 26 ± 5 mm Hg. None of these variables changed significantly in response to the increase in plasma NE levels from 730 ± 368 pg/ml (baseline) to 2,532 ± 1,326 pg/ml at the 2.5 μg/min level (Fig. 1). Plasma renin activity, 1.5 ± 0.54 ng/ml/hour, also did not change during the infusion.

These observations indicate that exogenous infusions of L-NE, which produce plasma levels comparable to those found during maximal exercise,[5] do not cause significant hemodynamic effects in patients with CHF. Silverberg et al[6] and Izzo (7) showed that in normal subjects, 2-fold or greater increases in plasma NE levels do raise blood pressure and reduce heart rate. Since with comparable or greater absolute and relative increases in plasma NE over baseline in heart failure we saw no hemodynamic changes, our data suggest a blunted peripheral vascular response to circulating NE in this condition with the lack of reflex bradycardia as a consequence.

A blunted blood pressure response to infused NE could be a consequence of "down regulation" of α_1-adrenergic receptors exposed to the chronically high levels of NE found in patients with CHF.[1,2] Such down regulation has recently been demonstrated in vascular smooth muscle.[8] Alternatively, the blunted response could be due to changes in number or sensitivity of peripheral α_2-adrenergic receptors, because they also may influence peripheral vascular resistance and may be more responsive to circulating as opposed to neuronally released NE.[9] Platelet α_2 receptors are decreased in CHF,[10] although we have no direct information concerning the postsynaptic α_2 receptor. Overall, down regulation of α receptors would not be surprising in

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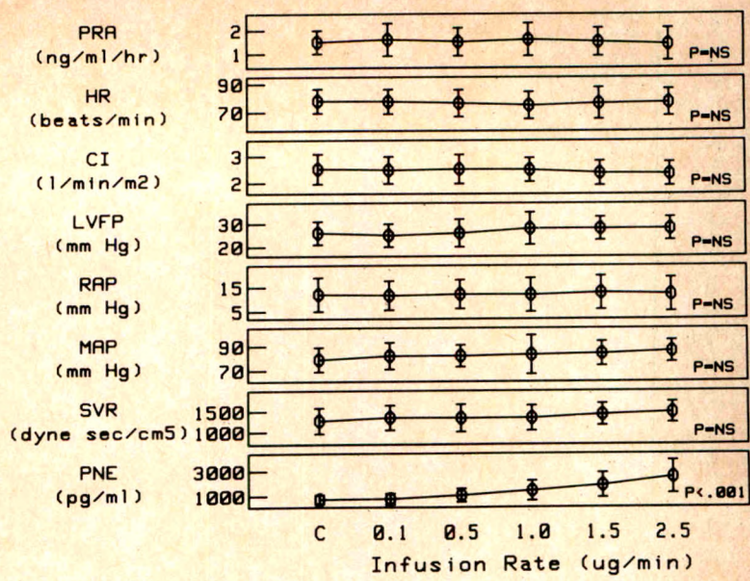

FIGURE 1. Response of plasma norepinephrine (PNE), plasma renin activity (PRA), heart rate (HR), mean arterial pressure (MAP), cardiac index (CI), systemic vascular resistance (SVR) and left ventricular filling pressure (LVFP) to exogenous norepinephrine infusions in patients with congestive heart failure (n = 8). Values are expressed as ± standard error of the mean. NS = not significant; RAP = right atrial pressure.

patients with CHF in view of the well documented down regulation of β receptors in this condition.[11,12]

The lack of hemodynamic effects during an exogenous NE infusion does not necessarily bear on the effects of endogenously released NE in patients either in the basal state or during stress. Plasma NE measured during endogenous stress represents only a small fraction of total NE released, because most is either taken up into the presynaptic nerve terminal or immediately metabolized in the synaptic cleft.[13] Hence, a given plasma level of NE produced by endogenous stress represents a much higher total NE response than that produced by an infusion. Nonetheless, these data do show that circulating NE itself, at the levels produced here, does not have a marked circulatory effect in patients with CHF. Any contribution of plasma NE as a circulating hormone to the vasoconstriction produced by a stimulus such as exercise is therefore likely to be minimal. The fact that vasoconstriction in nonexercising muscle beds does occur during exercise in patients with CHF,[14] strongly militates against another possible explanation for the current results—that NE-induced vasoconstriction is maximal or near-maximal in the basal state and therefore not amenable to further change by exogenously increased levels of circulating NE. Also in opposition to this interpretation is the observation that patients with CHF can respond in normal or even exaggerated fashion to infusion of another vasoconstrictor such as vasopressin.[15]

There was also no change in plasma renin activity during the infusions. Because plasma renin levels were essentially normal in this group of stable patients, it is unlikely that excessive baseline stimulation would account for the lack of response to the infused NE. Also, because there were no significant hemodynamic effects, a reflexly mediated decrease in renin activity probably did not offset any direct stimulation. Again, because synaptic cleft NE levels may be much higher than those in the plasma, circulating plasma NE levels in the range produced here may not be adequate to stimulate renin release by adrenergic mechanisms. However, as with the lack of vasoconstrictor response, an alternative possibility is down regulation of the renal β receptors responsible for mediating sympathetically induced renin release. This interpretation is buttressed by Izzo's study in normal subjects[7] in whom small changes in NE were associated with clear increases in plasma renin activity.

In summary, infusions of L-NE, which produced plasma NE levels of approximately 2,500 pg/ml, were without significant effects on either hemodynamic variables or renin activity in 8 patients with CHF. Although the role of endogenous sympathetic stimulation on hemodynamic variables and renin release is not resolved, the results do suggest a lack of any important effect on these variables from plasma levels of NE per se, and may point to altered peripheral adrenergic receptor activity in patients with this disease.

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Upright Paradoxical Posterior Wall Movement in Mitral Valve Prolapse

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JOSEPH KISSLO, MD

Upright exercise 2-dimensional echocardiography (2-D echo) is being used frequently to evaluate patients with suspected coronary artery disease (CAD).[1] As with other techniques, this diagnosis is suggested when segmental wall motion abnormalities appear with exercise. We have noted the spontaneous development of high posterior wall motion abnormalities during casual upright 2-D echo that were not present in the study during supine rest. These abnormalities appeared to be more obvious in patients with known or suspected mitral valve prolapse (MVP). This study documents the prevalence of a postural phenomenon in patients with MVP.

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Forty-six subjects were studied and were separated into 2 groups on the basis of the absence or presence of MVP by 2-D echo. MVP by 2-D echo was defined as systolic movement of 1 or both of the mitral valve leaflets into the left atrium and breaking the plane of the mitral valve anulus.[2] The non-MVP group consisted of 19 normal volunteers, aged 20 to 48 years (mean 33). The MVP group consisted of 27 persons, aged 22 to 45 years (mean 30), with definite auscultatory and 2-D echocardiographic evidence for MVP (15 with clicks alone and 12 with clicks and late systolic murmurs). No person had historical, physical or electrocardiographic evidence for CAD or any other form of heart disease and, except for findings of MVP, the 2-D echocardiographic results were normal. Except for 3 subjects with MVP who were receiving diuretic drugs, the study population was free from medication.

Complete 2-D echocardiographic examinations in all standard views were performed with the patient in the re-

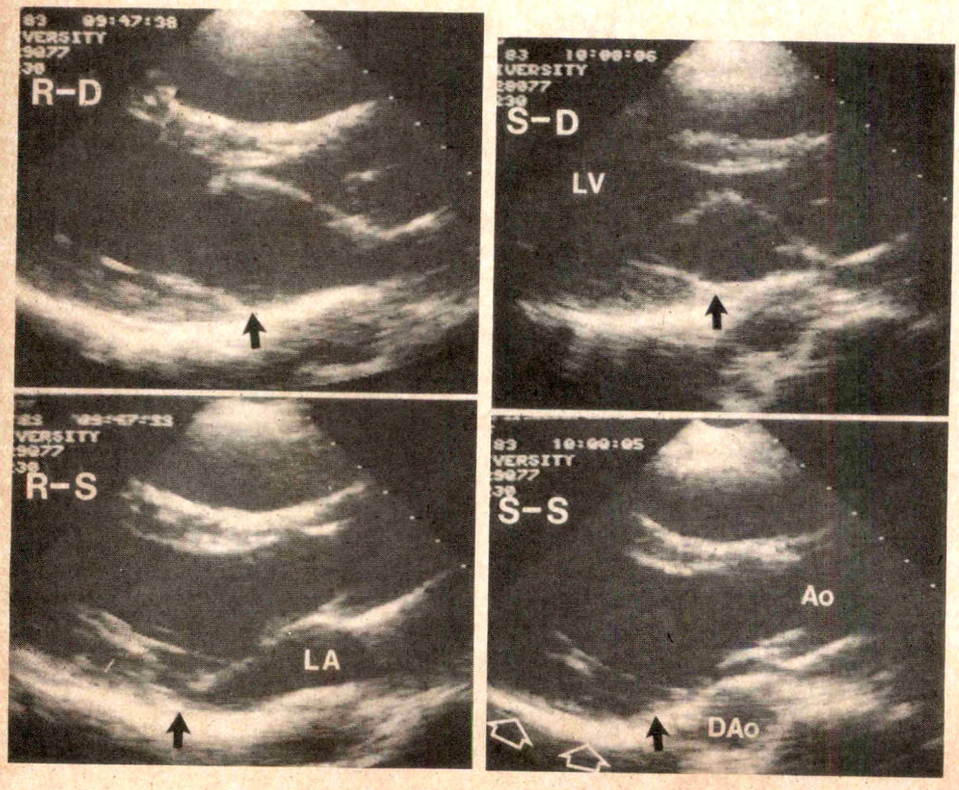

FIGURE 1. Composite long-axis recumbent views in diastole (R-D) and systole (R-S) as well as standing diastole (S-D) and systole (S-S) from a patient in group II, with more extensive changes during standing systole (**open arrows,** panel S-S). **Black arrows** indicate position of posterior mitral anulus. Ao = aortic root; DAo = descending aorta; LA = left atrium; LV = left ventricle.

cumbent, 30° left lateral and then upright positions using commercially available imaging systems with 3.5- or 2.5-MHz transducers. In addition, the last 6 MVP patients studied were also examined in the sitting position. Derived dual M-mode echocardiograms better displayed the induced wall motion abnormalities and were recorded while imaging in the parasternal long axis projection. Cursor A was placed through the high posterior ventricular wall just below the mitral valve anulus and cursor B was positioned through the left ventricular wall just above the papillary muscle. At no time did cursor A intercept the anulus or left atrium. All echocardiographic data were reviewed independently by 2 experienced observers and agreement by both as to the presence or absence of MVP and wall motion abnormalities was required.

All 19 normal subjects showed normal posterior wall motion in the recumbent position. Sixteen showed no change in the normal pattern of posterior wall motion when standing. However, 3 (16%) showed mild posterior wall dyskinesia when standing; 2 of them had equivocal MVP and 1 definitely did not have MVP.

Similarly, all 27 patients with MVP showed normal recumbent wall motion. When sitting, 4 of the 6 patients examined showed mild but obvious high posterior wall dyskinesia. Upon standing, every subject (100%) with MVP showed clearly evident dyskinesia of the high posterior wall (more severe compared with changes noted in the sitting position). In 21 patients, this abnormality was confined to the upper third of the posterior wall. In 6 patients, dyskinesia of the upper posterior wall was profound and extended more toward the ventricular apex (Fig. 1 and 2) and into the posterolateral wall.

This study shows that in patients with MVP and normal supine wall motion, significant posterior ventricular wall dyskinesia can develop when a standing position is assumed. Less significant dyskinesia can also be seen in some patients while sitting. In those in whom the subjective severity of the MVP was more severe, the extent and amount of dyskinesia was greater.

More than 20 years ago, Keats and Martt[3] made the initial flouroscopic observations of spontaneous high posterior wall motion abnormalities in the standing position. Inhomogeneity of normal left ventricular contraction has also been known for many years, with the high posterior wall showing later and less contractility compared with other wall segments in normal subjects.[4] The geometry and pattern of ventricular contraction can also be variable and dependent on volume loading conditions.[5,6] Few studies have closely examined wall motion changes occurring in upright posture, and since standing is accompanied by a decreased preload and chamber size,[7] some alteration of contractility and geometry may be expected.

Abnormal contractile patterns of the basal and posterior wall in the recumbent position are well recognized in some patients with MVP.[2,8,9] Abnormal biochemical and myocardial histologic characteristics have also been found.[10] No consensus exists, however, as to whether these changes represent a primary local myocardial problem or are induced secondary to MVP itself.

All subjects in the present study had normal wall motion in the supine position and all those with MVP had clear-cut dyskinesia from recumbent to standing positions. This phenomenon was probably not a result of positional artifact because dyskinesia was observed in more than 1 view. Similarly, we did not observe any recumbent/standing changes in electrocardiographic morphologic pattern to suggest an altered depolarization or conduction pattern.

This phenomenon may have multiple causes. First, decreased preload while standing may induce this phenomenon, given the many abnormalities associated with MVP (such as anular movement). Second, spatial geometric changes of the heart relative to other structures may be responsible. All subjects showed a decrease in left atrial size while standing, with an altered relation between left atrium and descending aorta. The mitral ring moved more inferiorly and posteriorly upon standing in patients with MVP than in normal subjects. In fact, the descending aorta impinged on the left atrial cavity from behind in some cases and appeared to restrict the movement of the anulus (Fig. 1). Third, the close proximity between taut chordae and endocardium may cause systolic mural compression.[9]

The results of this study have several important implications. As the use of 2-D echo in the sitting position or standing during upright exercise becomes more widespread, false-positive responses for CAD may occur unless the presence of MVP is suspected and these spontaneous changes are documented. The development of this abnormality also raises the possibility of an additional cause of the enhanced mitral murmur of

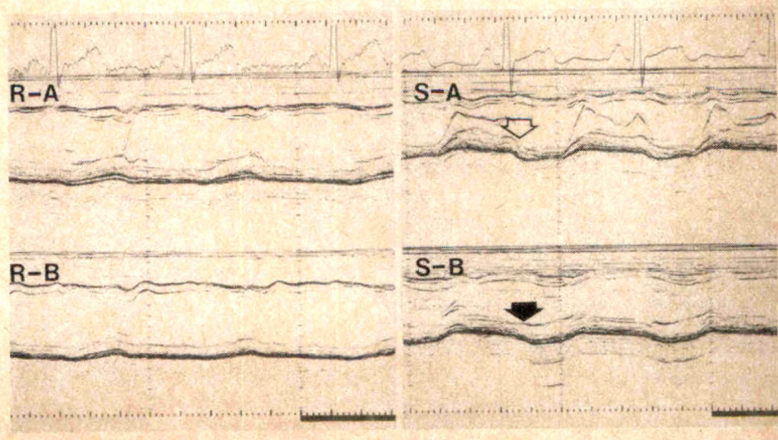

FIGURE 2. Dual M-mode traces from the same patient as in Figure 1, with normal posterior wall motion in the recumbent position (**left,** panel R-A). Upon standing (**right,** panel R-B), extensive paradoxic changes are noted in both the high (**open arrow,** S-A) and middle (**closed arrow,** S-B) back wall. R-A = recumbent just above papillary muscles; R-B = recumbent lower in ventricle; S-A = standing just above papillary muscles; S-B = standing lower in ventricle.

MVP on standing. Finally, the high incidence of the development of this dyskinesia in the upright position in patients with MVP suggests that it may be a useful provocative test for this entity.

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Safety of Labor and Delivery in Women with Mitral Valve Prolapse

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Because mitral valve prolapse (MVP) is associated with joint laxity, musculoskeletal abnormalities and distinctive anthropometric characteristics, and is present in most cases of the Marfan syndrome and the Ehlers-Danlos syndrome, the valve disorder probably represents the cardiovascular manifestation of a generalized disorder of connective tissue.[1] Fuenzalida[2] suggested that laxity of joints and connective tissue may facilitate pregnancy and childbirth, conferring a selective advantage to those who carry the MVP gene (or genes) and counteracting any natural selective presssure against the syndrome. Indeed, the gene appears to be most penetrant in women[3] and clinical aspects of this syndrome are most manifest during the childbearing years. Rayburn and Fontana[4] showed that pregnancy and childbirth were safe in women with MVP, but possible advantages of the syndrome were not examined. This study was designed to evaluate the ease and efficiency of labor and delivery in women with MVP.

The records of labor and delivery were evaluated in 23 patients with auscultatory and echocardiographic evidence for MVP, detected before the onset of labor, after 1981. All patients had abnormal findings on cardiac examination by their obstetrician and were therefore referred to a cardiologist. MVP was diagnosed if both a mid- to late apical systolic click or murmur was heard and M-mode echocardiography demonstrated at least 2 mm of pansystolic bowing or midsystolic buckling of the CD segment of the mitral tracing. A control was assigned to each patient, selected as the next patient delivering, matched for parity, age (within 2 years), race and infant birth weight (within 500 g). All control subjects had normal heart sounds on screening examinations by their obstetrician.

The rate of cervical dilatation during active labor, which accurately reflects the overall efficiency of labor,[5] was considered the major outcome variable. This value was determined by plotting cervical os diameter vs time (Freidman's curve) and measuring the rate at the maximal slope during the active phase of labor.[5] The duration of the first stage of labor was defined as the time between the onset of regular contractions and full cervical dilatation. The duration of the second stage of labor was measured from the time of full dilatation to delivery. For comparisons of infant birth weight and Apgar scores, a second group of control subjects was selected as above, except that infant birth weight was not matched. Weight before pregnancy and height were recorded and the ponderal index was calculated as the cube root of the body weight divided by the height, times 100. The highest systolic blood pressure during pregnancy was noted.

Statistical analysis was performed with paired t-tests, with pairs matched as described above, to facilitate control of variables known to influence the ease of labor and to isolate, as far as possible, the effects of MVP. Four pairs in which cesarean section or pitocin augmentation was required for either the patient or control were excluded in analysis of duration of labor and rate of cervical dilatation. Statistical power analysis was performed by the method of Young et al,[6] considering the rate of cervical dilatation at the maximal slope as the major outcome variable, with differences in the rate of dilatation of less than 2 cm/hour judged not to be of practical importance.

Patients with MVP weighed significantly less than control subjects and had a significantly lower ponderal index (Table I). The peak systolic blood pressure during pregnancy was 117 mm Hg in patients with MVP and 121 mm Hg in control subjects, but the difference was not statistically significant (2-tailed, $p = 0.07$). The rate of cervical dilatation at the maximal slope was 3.3 cm/hour in both patients and control subjects (difference not significant). With the given sample size and standard deviation, a difference of 1.1 cm/hour or greater could have been detected ($\alpha = 0.05$) with 80% certainty ($\beta = 0.20$).[6] The duration of the first and second stages of labor was not different in the 2 groups (Table I). Two patients and 1 control subject required cesarean section for breech presentation or failure of labor to progress. Two patients and 3 control subjects required pitocin augmentation. Birth weights and Apgar scores were similar in both groups. Thus, there were no statistically or physiologically signifi-

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TABLE I Characteristics of Labor and Delivery In Patients with Mitral Valve Prolapse and Matched Controls

	MVP (n = 23)	Controls (n = 23)	p*
Age (Yr)	22 ± 3	22 ± 3	NS (>0.5)
Height (inches)	65 ± 3	64 ± 2	NS (>0.5)
Weight (lbs)	112 ± 28	143 ± 33	0.002
Ponderal index	7.3 ± 1	8.1 ± 0.6	0.007
Parity	0.4 ± 0.7	0.4 ± 0.7	NS (identical)
Systolic BP (mm Hg)	117 ± 8	121 ± 12	NS (0.07)
Maximum slope of cervical dilatation (cm/hour)†	3.3 ± 1.2	3.3 ± 1.5	NS (>0.5)
Duration first stage (hours)†	8.4 ± 4.5	9.7 ± 6.5	NS (>0.5)
Duration second stage (hours)†	0.79 ± 0.8	0.61 ± 0.4	NS (0.26)
Duration first and second stage (hours)†	9 ± 5	10 ± 7	NS (>0.5)
No. requiring C-section	2	1	NS (>0.5)
No. requiring pitocin augmentation	2	3	NS (>0.5)
Birth weight (g)‡	3,231 ± 583	3,314 ± 477	NS (>0.5
Apgar (1 min/5 min)‡	7.8/9.1	7.7/8.9	NS (>0.5)

* Paired *t* tests or Fisher's exact test as required.
† Excluding patients with C-sections or pitocin augmentation.
‡ Compared to a second group of controls who were not matched for birth weight.
Values are mean ± standard deviation.
BP = blood pressure; C-section = cesarean section; MVP = patients with mitral valve prolapse; NS = not significant.

cant differences in the ease or efficiency of labor between these groups.

This study confirms that labor and delivery are safe in MVP, but provides no evidence for an advantage acting through joint laxity or distensible connective tissue during childbirth. The rate of cervical dilatation at the maximal slope provides an excellent measure of the overall efficiency of labor[5] and was used in this study as an indirect predictor of morbidity, since direct comparison of the rates of complications of labor, which are uncommon in our population, would have required very large sample sizes. Our inability to detect a difference is not likely a result of inadvertant dilution of the control group with patients with silent mitral valve prolapse, because the 2 groups showed expected differences in ponderal index and weight[7] and only patients with marked and unequivocal valvular abnormalities were selected for the study.

Differential fertility is an important agent of natural selection and is a logical consideration in justifying the high frequency of an inherited condition which predominately affects young women. Although we have shown no clinically significant advantage over the general population in the speed of labor and delivery, small differences which are not detectible by our methods could become important over very long time periods. Therefore, although not supported by our data, the hypothesis presented by Fuenzalida[2] cannot be absolutely excluded. Alternatively, any life-threatening complications associated with mitral valve prolapse may occur after the most fertile childbearing years in most instances, so that selective pressure against the syndrome is weak or nonexistent.

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Mitral Valve Prolapse and Addictions

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Mitral valve prolapse (MVP) is a common inherited disorder with a prevalence believed to be between 5 and 10% in the general population.[1] MVP is associated with an array of psychiatric diagnoses, including anxiety neurosis and panic attacks,[2] agoraphobia,[3] depression[4] and sleep disorders.[5] Autonomic dysfunction and elevation of plasma catecholamine levels have also been described,[6] suggesting that the valvular abnormality is part of a generalized neuroendocrine-cardiovascular disorder. During a 2-year period in a general hospital-based Substance Abuse Detoxification Unit, MVP appeared to occur more frequently than would have been expected in a randomly selected population. This report presents the results of a study designed to document the prevalence of MVP in patients who abuse psychoactive drugs and seek detoxification.

One hundred one consecutive patients (69 men, 32 women) were admitted to the Substance Abuse Detoxification Unit of Crouse Irving Memorial Hospital because of significant and continuing physical, interpersonal and occupational problems related to psychoactive drug abuse. They were 18 to 68 years old. All patients were unable to control use of addicting psychoactive drugs.

Fifty-six of the patients had systolic clicks with or without mid- to late systolic murmurs by auscultation in supine or standing positions. Of these 56 patients, 48 were then studied by 2-dimensional (2-D) and M-mode echocardiography using phased-array equipment (Toshiba model SSH10A or Hewlett Packard model 77020A) and 2.25-MHz transducer. The other 8 patients signed out against medical advice before echocardiographic study. Complete echocardiographic examination was performed using standard long- and short-axis views, as well as apical 4-chamber and subxiphoid positions. All studies were performed by experienced technicians with a senior cardiologist in attendance. The studies were reviewed for technical quality and further footage recorded by the cardiologist if necessary. M-mode records were derived from the 2-D examination and the data were used in the measurement of the cavity dimensions and wall thickness. MVP was diagnosed entirely on the basis of the 2-D study, following the criteria of Gilbert et al[7] and Morganroth et al.[8] When displacement of the anterior or posterior mitral leaflets or both was noted posterior to the mitral ring in either the long axis view or the apical four chamber view, MVP was considered to be present. All the records were reviewed by one of the investigators and MVP was diagnosed only when the above criteria were met.

Fifty-six patients had physical signs of MVP (mid- to late systolic click with or without systolic murmur), and 38 of these 56 patients had echocardiographic confirmation of the diagnosis. In the remaining 17 patients, the clinical evidence for MVP was not confirmed by echocardiography. However, 8 of these 17 left the hospital against medical advice before being studied. The occurrence of echocardiographically confirmed MVP in 37% of the patients admitted to the detoxification unit is substantially greater than the 5% to 10% prevalence of MVP expected in a randomly selected population.[1]

MVP was slightly less prevalent in the alcoholic patients than those admitted for abuse of other drugs (nonalcoholic sedatives, cocaine/amphetamines, opiates and multiple drug abuse) by the criteria of physical examination or echocardiography, but the number of patients in each group was too small for significant statistical analysis. Women admitted to our detoxification unit were more likely than men to have MVP by physical examination criteria ($p < 0.05$). This likelihood appears even more pronounced when echocardiographic criteria are used ($p < 0.025$). However, this may be influenced by the fact that 8 men but no women left the hospital against medical advice before being studied.

MVP may have been detectable by echocardiographic criteria in more than the 39 patients indicated in Table I. Some of the 45 patients with no clinical evidence for MVP likely had silent MVP. Further provocative testing with amyl nitrate was not done in the 9 patients with clinical evidence for MVP but negative echocardiographic findings. Finally, 8 patients with clinical evidence for MVP left the hospital against medical advice prior to being studied.

Patients with MVP often have associated dysphorias.[2–5] Vasomotor instability and elevation of plasma catecholamine levels have also been described.[6] Seeking relief from these symptoms, many patients with MVP enter the health care delivery system and are treated with medications such as β-blockers, antidepressants and sedatives. Addiction to sedatives, especially benzodiazapines, is a risk for these patients. The results of

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TABLE I Mitral Valve Prolapse and Addictions

	Detox Admissions			Alcohol Admission Subpopulation			Drug Admission* Subpopulation		
Manifestations of MVP	Total (n = 101)	Men (n = 62)	Women (n = 39)	Total (n = 57)	Men (n = 37)	Women (n = 20)	Total (n = 44)	Men (n = 25)	Women (n = 19)
No click	45(45%)	32(52%)	13(33%)	29(51%)	22(59%)	7(35%)	16(36%)	10(40%)	6(32%)
+ Click ± murmur	56(55%)	30(48%)	26(67%)	28(49%)	15(41%)	13(65%)	28(64%)	15(60%)	13(68%)
Signed out AMA before being studied	8(7%)	8(13%)	0(0%)	3(4%)	3(8%)	0(0%)	5(14%)	5(2%)	0(0%)
Studied by echo	48(46%)	22(35%)	26(67%)	25(46%)	12(32%)	13(65%)	23(52%)	10(4%)	13(68%)
+ Clinical exam but − MVP by echo	10(9%)	6(10%)	4(9%)	5(11%)	2(5%)	3(2%)	5(8%)	4(2%)	1(5%)
+ Click ± murmur and with MVP by echo	38(37%)	16(26%)	22(58%)	20(35%)	10(27%)	10(50%)	18(42%)	6(24%)	12(67%)

* Sedatives (other than alcohol), cocaine/amphetamines, opiates and multiple drug abuse.
AMA = against medical advice; Detox = detoxification; echo = echocardiogram; MVP = mitral valve prolapse.

this study suggest that some patients with MVP may self-medicate with psychoactive drugs in attempts to modulate some or all of these same dysphorias. Tolerance and loss of control supervene and, for many, addiction occurs.

Of the 39 patients with MVP documented by echocardiography, 23 had clear family histories of alcoholism (either parents, grandparents or aunts/uncles). This is consistent with studies that show that the offspring of alcoholics are more likely to have the same disease than the offspring of non-alcoholics. The role of environment in this issue has been minimized in Scandanavian adoption studies, and there is at least a 4 times increased risk for the adopted male offspring of an alcoholic biologic parent to develop alcoholism even when reared in homes where alcoholism is not present.[9] Further, behavioral and neurochemical studies have shown that certain genetic strains of mice prefer and seek out alcohol in laboratory feeding selections and become addicted when compared to other strains of mice. These addiction-prone mice have baseline deficiencies in whole brain met-enkephalin.[10]

Thus, there is evidence for a genetic neuroendocrinologic basis for the inability to control appetite for psychoactive drugs. MVP may be a marker for an increased risk of developing substance abuse and addiction. Further study directed toward identifying endorphin abnormalities in the disorder of MVP and in addiction-prone families may lead to a greater understanding of the personality prone to addiction.

This study suggests that patients with MVP are overrepresented in the population of substance abusers requiring detoxification. Practitioners should try to identify these patients in order to evaluate and counsel them regarding symptoms and complications of the MVP syndrome. Particular attention should be paid to the risks of using intravenous drugs in patients with MVP because of the inherent risks of developing infective endocarditis.

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Significance of E Point–Septal Separation by M-Mode Echocardiography in Patients with Aortic Regurgitation

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Separation between the mitral E point and left side of the ventricular septum on M-mode echocardiography has been shown to be a practical index of left ventricular (LV) performance in adults and children with unrestricted motion of the mitral valve.[1–4] Patients with aortic regurgitation (AR) are usually excluded from studies of E point–septal separation (EPSS) because of the possibility of abnormal mitral valve motion, and echocardiography performed on a few of these patients has revealed no consistent relation to contractile function.[1] To evaluate the significance of EPSS in this disorder, we retrospectively examined M-mode echocardiograms of 56 patients who underwent cardiac catheterization for AR.

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The records of all adult patients who underwent cardiac catheterization at Montefiore Medical Center between December 1974 and April 1984 were reviewed. Fifty-six patients with isolated moderate or severe AR, 37 men and 19 women between ages 19 and 84 years, had technically adequate echocardiographic and angiographic studies. Patients were excluded if either the M-mode echocardiogram or angiogram was inadequate, or if mitral stenosis, mitral regurgitation, aortic stenosis or pulmonary hypertension (pulmonary artery systolic pressure 55 mm Hg or greater) coexisted.

Echocardiograms were performed with either an Irex 101 M-mode echocardiograph and 2.25-MHz transducer coupled to a Honeywell strip-chart recorder or a Hoffrel model 101 ultrasonoscope. Patients were studied in the left lateral decubitus position with varying degrees of rotation. The mitral valve was recorded at the position where both leaflets were visualized and mitral excursion was greatest. Studies were excluded if either the left side of the septum or mitral valve was poorly visualized, or if marked diastolic fluttering of the anterior mitral leaflet obscured the E point. EPSS 1 was defined as the vertical distance from the leading edge of the left septal echo to the simultaneously recorded leading edge of the mitral valve at its most anterior position in early diastole (Fig. 1). EPSS 2 was defined as the vertical distance from a horizontal line drawn through the left side of the

septum at its most posterior position in the cardiac cycle to the mitral valve E point (Fig. 1). EPSS was evaluated in 10 consecutive beats, and the minimal value was accepted.

Cardiac catheterization was performed within 15 days of echocardiography, and in most cases it was done the next day. Biplane angiography was performed in the right and left anterior oblique projections. Left ventricular systolic and diastolic volumes were calculated using the Dodge method.[5] *In 43 patients, cardiac output was determined by the Fick method.*

Fifty-six subjects with moderate or severe AR had technically adequate angiograms and echocardiograms, and no evidence of other significant valvular lesions. EPSS 1 exceeded EPSS 2 by 4 to 7 mm in 9 patients. In all other patients, EPSS 1 was 0 to 3 mm greater than EPSS 2.

Nineteen of 56 patients (34%) had an ejection fraction (EF) greater than 55% with EPSS more than 10 mm. Figure 1 is a representative mitral valve echogram in a patient with severe AR secondary to a biscuspid aortic valve. Despite a normal EF of 62%, EPSS is greatly increased to 30 mm. Cardiac output and LV end-diastolic pressure were both normal in this patient. For all patients studied, the relation between EPSS 1 and LV function as assessed by angiographic EF is shown in Figure 2. Linear regression analysis yielded a poor negative correlation between EPSS and EF, with $r = -0.48$ for EPSS 1 and $r = -0.47$ for EPSS 2. No value for EPSS clearly separated patients with normal and abnormal EF. Among 20 patients with depressed EF, however, only 3 had normal EPSS.

Figure 3 shows the relation between EPSS 1 and LV end-diastolic volume in 46 patients in whom this volume was quantitated. Although there is a tendency for greater LV volume to be associated with higher EPSS, correlation was poor ($r = 0.57$). Using EPSS 2, $r = 0.61$. No value for EPSS classified patients into groups with mildly and severely increased LV end-diastolic volumes, although all patients with volumes greater than 305 ml had EPSS of at least 15 mm. Among 43 patients in whom cardiac output was determined, there was no correlation with EPSS ($r = -0.04$). EPSS 1 exceeded 10 mm in 55% of patients with fluttering of the mitral valve by echocardiography and in 56% of those without fluttering.

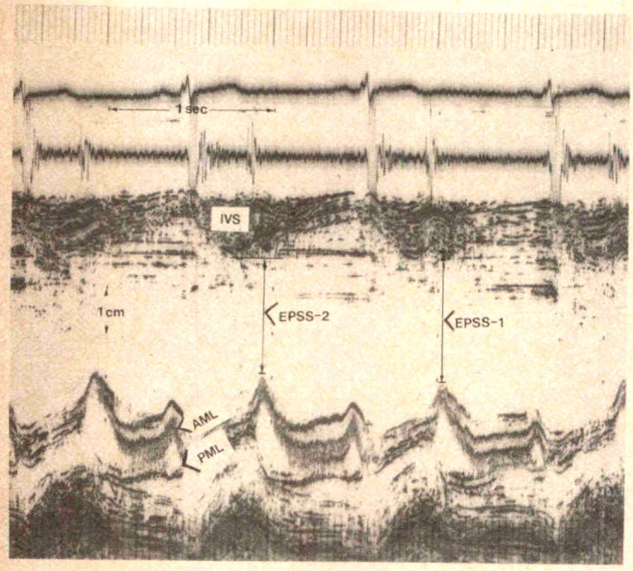

FIGURE 1. M-mode echocardiogram at the level of the mitral valve in a patient with severe aortic regurgitation, illustrating the method used to measure E point-septal separation (EPSS) 1 and EPSS 2. This patient had an ejection fraction of 62%, but EPSS 1 and 2 were increased to 30 and 28 mm, respectively. AML = anterior mitral leaflet; IVS = ventricular septum; PML = posterior mitral leaflet.

Although increased EPSS appears to be associated with larger ventricles and poorer systolic function in patients with AR, correlation is poor for individual patients. In 1977, Massie et al[1] described the association of increased EPSS and reduced LV systolic function in patients with no AR or mitral stenosis, and found that a value of at least 5 mm for EPSS 1 correlated strongly (r = 0.87) with reduced angiographic EF. D'Cruz et al[2] and Lew et al[3] later suggested EPSS up to 6 mm was normal, and confirmed the association between increased EPSS and LV dysfunction. Child et al[4] compared patients with MR and no LV failure with those having either dilated or amyloid cardiomyopathy, and found that EPSS of at least 6 mm accurately identified

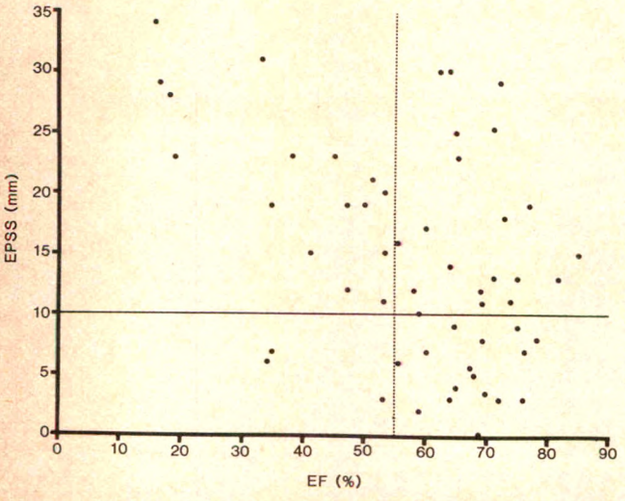

FIGURE 2. Relation of E point-septal separation (EPSS) 1 to angiographic left ventricular ejection fraction (EF) in patients with moderate to severe aortic regurgitation. Correlation between these parameters is weak (r = −0.48).

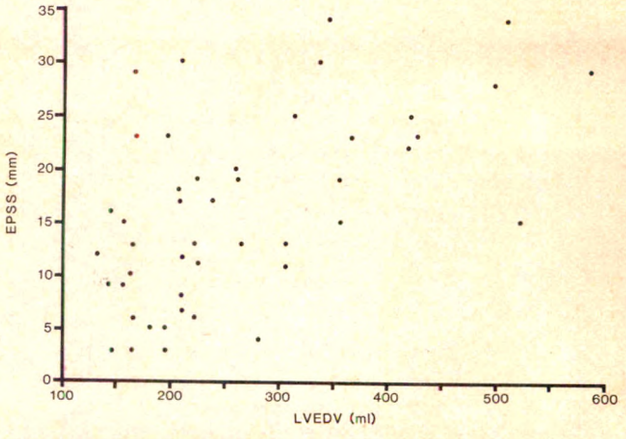

FIGURE 3. Relation of E point-septal separation (EPPS) 1 to angiographic left ventricular end-diastolic volume (LVEDV) in patients with moderate to severe aortic regurgitation. There is weak correlation between these parameters (r = 0.57).

patients with EF less than 55%, irrespective of LV size, although patients with dilated cardiomyopathy tended to have greater EPSS than those with restrictive disease.

We chose to define EPSS as the instantaneous vertical distance from the left side of the ventricular septum to the E point, and compared these measurements with those derived by the method described by Massie et al.[1] Since the original M-mode studies were done, 2-dimensional echocardiography has demonstrated that motion of the heart within the thorax causes the wall segments imaged by M-mode tomography to vary during the cardiac cycle.[6] Simultaneous EPSS, therefore, may be expected to be a more accurate reflection of the distance between the septum and mitral valve. There was no significant difference in correlation between LV volume or EF and EPSS measured by either method.

One explanation for the poor correlation between EF and EPSS is chamber dilatation secondary to AR. If this were the case, however, correlation between diastolic volume and EPSS might be expected to be stronger. In some cases, marked fluttering of the anterior mitral leaflet in the presence of AR might have obscured the true E point. However, we eliminated those studies in which a well-defined E point could not be identified. The incidence of increased EPSS was equal in patients with and without fluttering. It is also possible that some of the patients with severe AR and normal EF had reduced LV contractility. In these patients, EF could seemingly have been preserved because of the independent influence of increased preload and ventricular dilatation. Cardiac output, however, does not appear to significantly influence EPSS in patients with AR.

Impingement of the aortic jet on the body of the anterior mitral leaflet appears to cause the leaflet to bow away from the septum as the valve opens.[7] This is likely to account for observations of abnormal EPSS in patients with normal EF.

In conclusion, EPSS is not a useful predictor of LV function or dilatation in individual patients with AR, although greater EPSS tends to be seen in those patients with larger left ventricles and reduced EF.

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Auscultation, M-Mode Echocardiography and Pulsed Doppler Echocardiography Compared with Angiography for Diagnosis of Chronic Aortic Regurgitation

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Pulsed Doppler echocardiography (PDE), which detects velocity, timing and direction of blood flow, is both sensitive and specific in detecting aortic regurgitation (AR) and appears to be superior to more standard noninvasive techniques.[1] In our study, 3 noninvasive means of detecting AR—cardiac auscultation, M-mode echocardiography (echo) and PDE—were compared with aortography.

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Twenty patients (9 men, 11 women, aged 27 to 76 years) underwent cardiac catheterization for evaluation of either mitral or aortic valve disease. Aortograms were reviewed by an investigator blinded to the results of noninvasive studies, who estimated AR severity using the technique of Grossman and Dexter.[2] Echocardiographic and PDE studies were usually performed before angiography (27 ± 30 days, range 2 to 84) on a Honeywell Ultra-Imager duplex echocardiograph with transducer frequencies of 2.5, 3.5 and 5.0 MHz by technicians blinded to the results of auscultation and angiography. No attempts were made to control ventricular loading conditions. M-mode echocardiograms were recorded at a scan speed of 50 mm/s from the standard parasternal position. Pulsed Doppler echocardiograms were recorded from 3 standard positions (parasternal long axis, apical 4-chamber and apical long axis) with the Doppler sampling site positioned in the left ventricular outflow tract just below the aortic valve under 2-dimensional echocardiographic guidance. The Doppler signal was recorded in both video and audio formats using a Honeywell VGR 4000 video graphics recorder.

An investigator blinded to the results of all other studies evaluated the echocardiographic and, separately, PDE results. AR was not quantitated. Two weeks later, the original reviewer and another investigator, blinded to prior interpretations, independently reviewed all PDE studies. The final PDE diagnosis was based on the consensus of these 3 independent interpretations. High-frequency diastolic fluttering of the mitral leaflets, chordae tendineae, or left

TABLE I Comparative Results

	Aortogram	Auscultation	Echo	PDE
TP	11	6	5	10
FP	. . .	0	0	0
TN	9	9	7	9
FN	. . .	5	5	1
Total	20	20	17	20
Sensitivity		54% (6/11)	50% (5/10)	91% (10/11)
Specificity		100% (9/9)	100% (7/7)	100% (9/9)
Positive predictive value		100% (6/6)	100% (5/5)	100% (10/10)
Negative predictive value		65% (9/14)	58% (7/12)	90% (9/10)
Diagnostic accuracy		75% (15/20)	71% (12/17)	95% (19/20)

Echo = M-mode echocardiography; FN = false negative; FP = false positive; PDE = pulsed Doppler echocardiography; TN = true-negative; TP = true positive.

ventricular surface of the ventricular septum served as the echocardiographic marker of AR. AR was diagnosed if PDE showed spectral broadening with a duration of longer than 0.10 second and a peak velocity of more than 20 cm/s, suggesting turbulent, apically directed, diastolic blood flow in the left ventricular outflow tract.

The sensitivity, specificity, predictive values and accuracy of the noninvasive techniques were calculated relative to angiography (Table I). AR was detected angiographically in 11 patients; it was mild (1 to 2+) in 8 patients and moderate (3+) in 3. M-mode echocardiograms were recorded in 17 patients. Of the 8 patients with mild AR, auscultation detected AR in 3, M-mode echo detected it in 4 and PDE detected it in 7. In the 3 patients with moderate (3+) AR, both PDE and auscultation were 100% sensitive. M-mode echo failed to detect AR in 2 of these patients, both of whom had mitral stenosis. Doppler interpretation was based on only 1 transducer position in 11 patients and 2 positions in 5. Both inter- and intraobserver variation with PDE were 5%.

Auscultation produced 5 false-negative studies, 4 of which occurred in patients with mild AR. Of the 5 false-negative echocardiographic studies, 4 occurred in patients with mitral stenosis and 1 in a patient with mild AR. Only 1 false-negative diagnosis resulted from PDE, in a patient with mild, isolated AR. There were no false positive results from any method.

Our data, like those of Saal et al,[1] show that neither cardiac auscultation nor M-mode echo is sensitive for detecting AR (especially when mild) in contrast to PDE. In studies comparing auscultation and M-mode echo,[1,3] both had sensitivity of less than 80%, whereas in noncomparative studies, PDE had a sensitivity of 92 to 100%.[4,5] The low sensitivity of auscultation may stem, in part, from the difficulty in appreciating the faint, high-pitched murmur when AR is mild or, to a lesser extent, in the presence of the murmur of mitral stenosis. Similarly, the low sensitivity of M-mode echo may be largely attributed to mitral stenosis where leaflet thickening dampens diastolic leaflet flutter.[3,6] Either mild AR or mitral stenosis account for all the false-negative studies with auscultation and echo in our series. Our experience confirms that PDE is superior to both auscultation and M-mode echo in detecting AR (especially mild AR) and is not limited by mitral stenosis.

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Left Atrial Mobile Thrombus in Hypertrophic Cardiomyopathy

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Atrial fibrillation (AF) and low cardiac output are closely related to the occurrence and development of left atrial (LA) thrombi. Some investigators[1–3] reported that AF was observed in 5 to 15% of patients with hypertrophic cardiomyopathy (HC). Henry et al[4] reported that AF was observed in more than 40% of patients with asymmetric septal hypertrophy and LA dimension of 40 mm or greater. To our knowledge, however, no patient has been described with HC who had a LA mobile thrombus. We present 2 such patients.

Case 1: *A 52-year-old man treated for HC was admitted 2 days after sudden onset of palpitation and chest discomfort. The blood pressure was 94/76 mm Hg. An electrocardiogram revealed AF with high R voltages and negative T waves*

in the precordial leads. After 3 days of hospitalization, AF returned to sinus rhythm with disopyramide therapy and bed rest. Two-dimensional echocardiograms (Fig. 1) revealed LA mobile thrombus occurring in the vicinity of the LA appendage. An echocardiogram recorded 3 months before admission showed a marked increase in ventricular septal thickness but did not show a thrombus. Cardiac index, measured by the dye-dilution method, was 2.3 liters/min/m^2 (Table I).

Case 2: *A 49-year-old man with a history of recurrent faintness was admitted complaining of palpitation and general malaise. The blood pressure was 92/70 mm Hg. An*

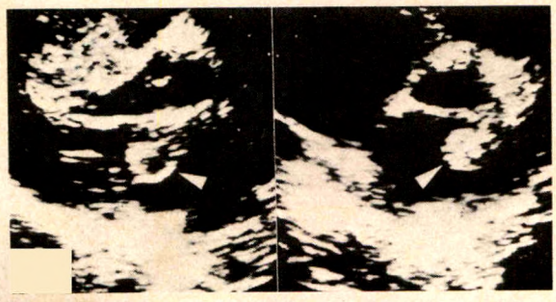

FIGURE 1. Long-axis (**left**) and short-axis (**right**) 2-dimensional echocardiograms from patient 1. A mobile thrombus (**arrow**) was observed in the left atrial cavity. During the cardiac cycle, the thrombus was most clearly observed from late diastole to early systole (**left**). From the short-axis echocardiographic observation, the thrombus was seen to occur in the vicinity of the left atrial appendage (**right**).

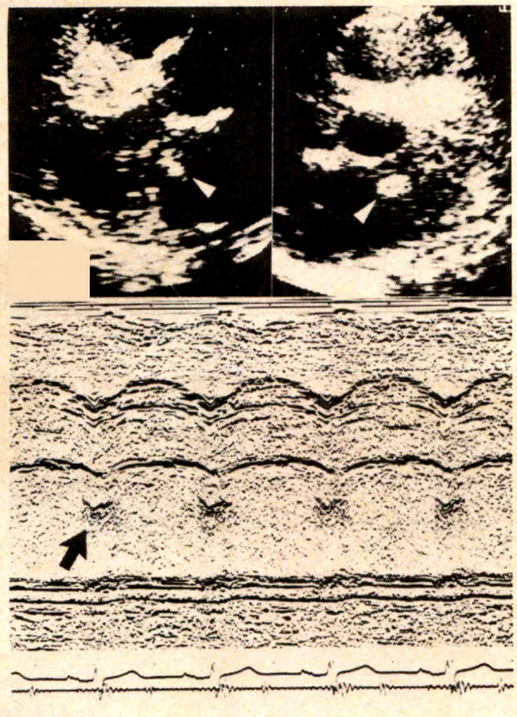

FIGURE 2. Two-dimensional and M-mode echocardiograms from patient 2. In the long-axis 2-dimensional echocardiogram, a thrombus was most clearly observed at early systole (**top, left**). From the short-axis echocardiographic observation (**top, right**), the thrombus occurred in the vicinity of the left atrial appendage as seen in patient 1. In the M-mode echocardiogram (**bottom**), the thrombus (**arrow**) was also recognized from end-diastole to early systole in the left atrial cavity.

TABLE I Hemodynamic and Echocardiographic Measurements

Pt	HR (beats/min)	SBP/DBP (mm Hg)	CI (liters/min/m^2)	SI (ml/beat/m^2)	TPRI (dynes s cm^5)	LVDd (mm)	LVDs (mm)	LAD (mm)	VS (mm)	PWT (mm)	VS/PWT	SAM	MSC
1	58	100/68	2.3	40	2,745	42	29	41	22	10	2.2	+	+
2	52	116/70	1.9	37	3,575	38	25	44	29	14	2.1	–	+

CI = cardiac index; HR = heart rate; LAD = left atrial dimension; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; MSC = midsystolic closure of the aortic valve; PWT = left ventricular posterior wall thickness; SAM = systolic anterior motion of the mitral valve; SBP/DBP = systolic/diastolic blood pressure; SI = stroke index; VS = ventricular septal thickness; + = present; – = absent.

electrocardiogram showed AF with negative T waves in leads V_5, V_6, I and aVL. After 5 days of the hospitalization, AF returned to sinus rhythm, but soon after he complained of severe ache in his left leg owing to embolic complication. Echocardiograms showed marked ventricular septal thickening and a mobile thrombus occurring in the vicinity of the LA appendage (Fig. 2). The patient showed not only reduced cardiac index, but also markedly elevated total peripheral resistance index (Table I).

During the cardiac cycle, the thrombi observed in 2 patients showed the same pattern of motion that was observed most clearly from end-diastole to early systole. Emergency cardiac surgery was performed in both patients and thrombi were removed. In addition, to prevent formation of the LA thrombus, plication of the LA appendage was performed. Diastolic compliance failure of HC appeared to be the main cause of AF. The combination of stagnant blood flow due to AF and low cardiac output appeared to predispose to thrombus formation.

Acknowledgment: We thank Yo Osuga, MD, for performing the corrective surgery.

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Acute Left Ventricular Dysfunction and Thrombosis Following Natural Gas Poisoning

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Left ventricular (LV) thrombus formation is a recognized complication of myocardial infarction[1] and of dilated cardiomyopathy,[2] but to our knowledge, it has not previously been reported in association with hypoxia-related reversible LV dysfunction. We describe such a case.

A 19-year-old woman was admitted to the hospital after accidental gas poisoning over approximately 12 hours. Initial resuscitation with oxygen reversed deep cyanosis and improved mental state from coma to stupor. The blood pressure was 90/60 mm Hg, heart rate 140 beats/min, respiratory rate 40 breaths/min and temperature 38.5°C. The patient weighed 50 kg. She was mildly dehydrated and had a prominent gallop rhythm. Arterial blood gases after initial resuscitation showed hypoxia (PO_2 55 mm Hg with oxygen 40%) and mild metabolic acidosis (pH 7.36, bicarbonate 14 mmol/liter). Carboxyhemoglobin was mildly elevated at 12.7% (normal 0 to 1.5%, with cerebral symptoms evident above 30%). Chest x-ray showed normal heart size and clear lung fields. An electrocardiogram showed sinus tachycardia.

The clinical course was one of progressive improvement of mental status with supplemental oxygen, intravenous rehydration, dexamethasone, 16 mg, amoxicillin and chest physiotherapy. Despite resolution of fever, the gallop rhythm and a tachycardia of 120 beats/min persisted at the end of 24 hours. Blood and urine cultures were sterile. Creatine kinase-MB fraction was not elevated, but an electrocardiogram showed widespread nonspecific ST-T changes with T-wave flattening. An echocardiogram was performed within 24 hours of admission. The left ventricle was mildly dilated (end-systolic diameter 40 mm [normal 28 ± 6 mm], end-diastolic diameter 51 mm [normal 44 ± 6 mm]) with reduced fractional shortening (22% [normal 26%]). All valves appeared intrinsically normal, but interrupted aortic valve closure and a "B" notch on the mitral valve trace were consistent with elevated LV end-diastolic pressure. The 2-dimensional echocardiogram also confirmed mild global cardiac enlargement and reduced contraction with an ejection fraction of 40% (based on single-plane ellipsoid formula for LV volume). Within 4 days, mental function had returned to normal, the gallop rhythm was absent and tachycardia resolved to an awake heart rate at rest of 80 beats/min. A repeat echocardiogram 4 days later showed normalization of LV dimensions (end-systolic diameter 30 mm, end-diastolic diameter 47 mm) and fractional shortening (36%). On the 2-dimensional sector scan, ventricular size and function appeared normal but an apical thrombus measuring 10 mm in diameter was clearly demonstrated in multiple views and at various depth and gain settings (Fig. 1).

The 2 most striking aspects of this case are the prompt resolution of the initial clinical and echocardiographic features of severe myocardial dysfunction, and the unexpected discovery of an apical LV thrombus on the predischarge echocardiogram. The speed of recovery of myocardial function suggests that no significant intrinsic myocardial damage was sustained but rather that a "stunned" myocardium[3] was responsible for the reversible dysfunction. The constituents of

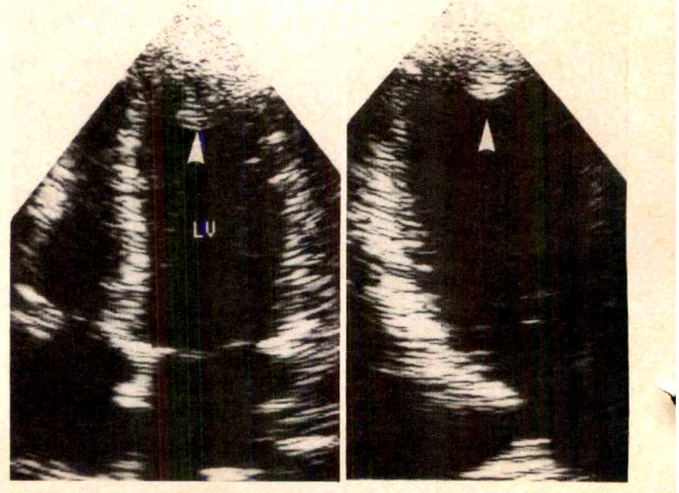

FIGURE 1. Left, apical 4-chamber view demonstrating thrombus (**arrow**) in left ventricular (LV) apex. **Right,** apical 2-chamber view demonstrating LV thombus (**arrow**).

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natural gas (predominantly methane, and small to trace amounts of other hydrocarbons, nitrogen, carbon dioxide and mercapto compounds) are not known to have direct myocardial toxicity[4] in the concentrations encountered; thus, hypoxia rather than toxicity must be considered the responsible mechanism.[5]

The hypoxic myocardial dysfunction in this patient was completely reversible, although in the interim an LV thrombus had formed rapidly and thus may complicate any form of acute cardiomyopathy.

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Massive Endocardial Calcification Associated with Endomyocardial Fibrosis

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Silver et al[1] described massive mural calcific deposits as a newly recognized cause of impairment to left ventricular filling. We present 2 patients with massive endocardial calcification who also had typical features of nontropical endomyocardial fibrosis (EMF).

Patient 1: *A 53-year-old woman had bronchial asthma since early childhood. Six months before admission atrial fibrillation developed with severe exertional and nocturnal dyspnea and a 3/6 holosystolic apical murmur. Chest x-ray showed a conspicuous calcification (Fig. 1.). Two-dimensional echocardiography (2-D echo) revealed massive calcification on the endocardium at the left ventricular apex, the distal third of the septum and the posterior wall and on both papillary muscles. Cardiac catheterization and angiography disclosed a typical "ace of hearts"–shaped left ventricle massive mitral regurgitation and elevated (22 mm Hg) left ventricular end-diastolic and pulmonary artery pressure (62/30 mm Hg) (Fig. 2.). At surgery, masses of friable and partly calcified thrombi and parts of the calcified endocardium were removed (Fig. 3), and the mitral valve was replaced. Cardiac catheterization 6 months postoperatively revealed a left ventricular end-diastolic pressure of 11 mm Hg and pulmonary arterial pressure of 37/17 mm Hg.*

Patient 2: *A 42-year-old woman with a history of helminthiasis was studied because of progressive dyspnea. Two-dimensional echo showed massive calcification of the left ventricular endocardium primarily at the region of the apex and the septum, an obliterated right ventricular apex and dilated atria (Fig. 4). Cardiac catheterization and angiography revealed elevated left and right ventricular end-diastolic pressures, mild tricuspid regurgitation and right ventricular apical obliteration. Over a follow-up period of 1 year, medical treatment has kept this patient in functional class II.*

We have seen 9 patients with eosinophilic EMF with or without eosinophilia over the last 6 years, and 8 of them underwent operation. The 2 patients just described had characteristic clinical, 2-D echo, hemodynamic and angiographic signs of EMF without eosino-

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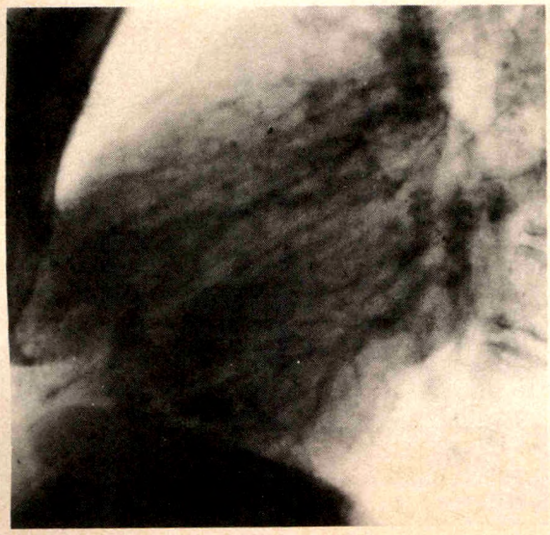

FIGURE 1. Intracardiac calcification on chest x-ray in patient 1.

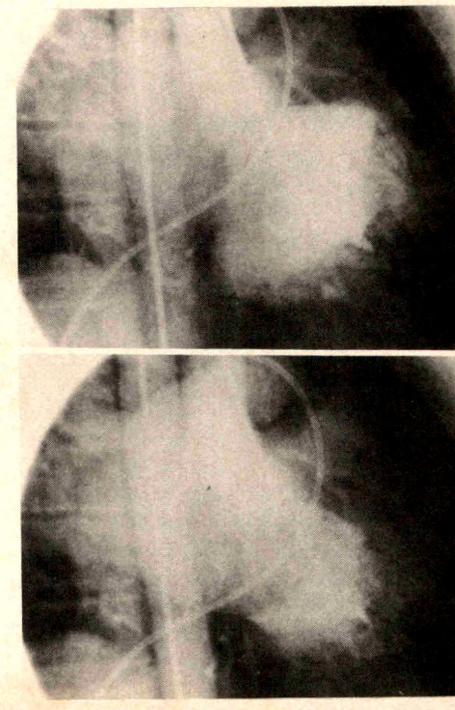

FIGURE 2. Left ventricular angiogram in patient 1 showing a typical "ace of hearts"–shaped left ventricle and massive mitral regurgitation. **Top,** diastolic and **bottom,** systolic frames.

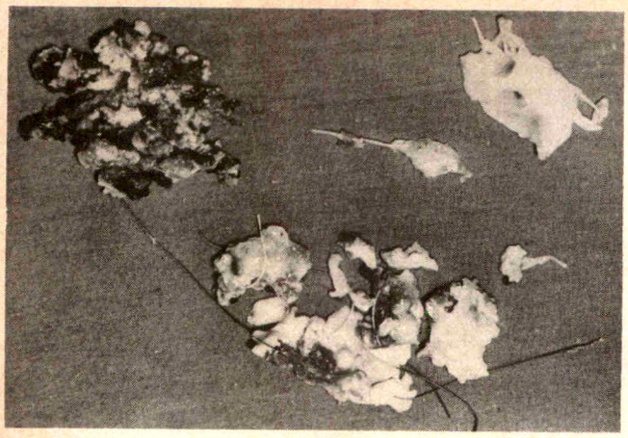

FIGURE 3. Masses of calcified and friable thrombi, calcified endocardium and a pliable mitral leaftlet removed at surgery from patient 1.

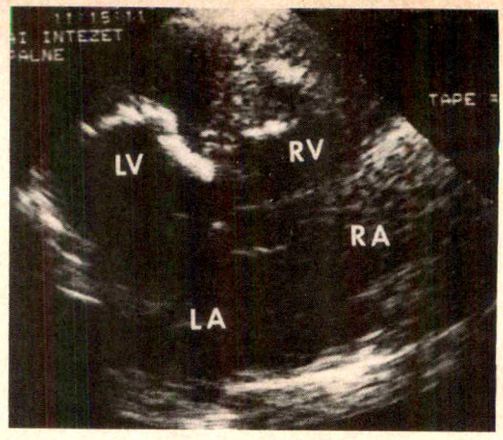

FIGURE 4. Two-dimensional echocardiogram obtained in the apical 4-chamber view in patient 2. There is massive calcification of the septum of the left ventricular apex and, to a lesser degree, of the right ventricular apex. Both atria are dilated. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

philia. Patient 1 also had morphologic signs of EMF without eosinophilia. They may have had eosinophilia in the earlier course of their disease, associated with parasitic infection in 1 patient and asthma in the other. In addition, they had massive calcification of the endocardium of the left ventricle. Our observations thus do not seem to support the view that massive calcification represents an entity independent of EMF.[1] On the contrary, these 2 cases confirm previous observations and support the opinion that extensive, widely distributed calcific deposits may be present within the left ventricular cavity in patients with EMF.[2–6] Endocardial calcification in these cases may be the diagnostic clue calling attention to the probable presence of EMF.

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Effect of Intense Aerobic Training on Exercise Performance in Children After Surgical Repair of Tetralogy of Fallot or Complete Transposition of the Great Arteries

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The role of rehabilitation after surgical repair of cyanotic congenital heart defects in children is unclear. Although highly effective cardiac rehabilitation programs exist for adults with acquired cardiac disease, few are available for children.[1,2] Hemodynamic and electrophysiologic disturbances are often present after surgical repair of congenital heart lesions. Diminished right and left ventricular compliance[3] and late dysrhythmias[4] are seen after the Mustard operation for complete transposition of the great arteries (TGA). Patients with repaired tetralogy of Fallot (TF) may have abnormal right and left ventricular function[5] and ventricular arrhythmias.[6,7] Further, exercise capacity is known to be subnormal in children following repair of TGA[3] and TF.[8] We report the effects of a monitored aerobic training program on children who had undergone operative repair of TGA or TF to determine the magnitude of potential improvement in aerobic fitness and to develop a scientific basis for rational exercise guidelines.

Eleven patients were selected for participation in the study because of the nature of their lesions and their proximity to the hospital. Nine of 11 patients completed the program and form the basis of this report (Table I). All 9 patients had undergone operative repair more than 2 years before the program began.

The 5 patients in the TGA group had undergone Mustard's operation 4 to 11 years earlier (mean 7.11) at a mean age of 10 months. Three of the 5 patients required subsequent pacemaker implantation for dysrhythmia management and 2 required digoxin and propranolol therapy. Postoperative cardiac catheterization data were available in 4 of 5 patients. All had a normal cardiac index at rest, normal right ventricular end-diastolic pressure and normal pulmonary vascular resistance. Angiographically, none had tricuspid

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TABLE I Patient Profile

Pt	Age (yr) & Sex	Diagnosis	Pace-maker	Intracardiac Pressures (mm Hg) RA	RV	PA	LV	Angiography
1	7.0F	TF	+					
2	13.0M	TF	0	5	40	25/10	120/10	Mild PR
3	6.0M	TF	0	5	30	30/5		Severe PR
4	6.0M	TF	0	7	60	17/5	95/5	Moderate PR, Moderate PS
5	7.0M	TGA	+	2	100	16/4	35/3	↓RV contractility
6	5.0M	TGA	0					RV contractility normal
7	12.0M	TGA	+	7	100	22/12	40/5	↓RV contractility
8	4.5M	TGA	0	4	90	30/5		RV contractility normal
9	12.0F	TGA	+					

LV = left ventricular; PA = pulmonary artery; PR = pulmonary regurgitation; PS = pulmonary stenosis; RA = right atrial; RV = right ventricular; TGA = transposition of the great arteries; TF = tetralogy of Fallot.

TABLE II Effects of Pediatric Cardiac Rehabilitation

	Weight (kg)		HR (beats/min)		$\dot{V}E$ (liters/min)		BP (mm Hg)		TT (min)		$\dot{V}O_2$ (ml/kg/min)	
Pt	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	19.5	19.5	188	190	30.0	34.8	125	140	14.3	19.5	42.1	55.0
2	39.0	39.0	214	214	64.2	64.7		160	11.0	13.5	40.0	52.3
3	22.0	22.0	192	188	41.8	42.6	122	140	16.0	16.5	50.0	54.5
4	23.0	23.0	150	188	25.6	44.5	124	140	12.0	18.0	38.7	57.1
5	27.0	27.0	150	167	33.1	27.0	118	140	8.0	9.0	38.9	36.0
6	23.0	23.0	150	167	20.3	23.0	115		14.0	14.0	20.0	36.0
7	44.0	41.0	115		26.6	30.1	104	130	6.0	8.0	22.0	27.5
8	18.0	18.0	170	167	31.0	27.4	106	130	14.0	16.0	42.7	39.4
9	23.0	25.0	150	167	41.2	37.1		140	10.0	13.0	41.3	50.1
Mean	26.5	26.4	164	181	34.8	36.8	116	140	11.7	14.2	37.4	45.2
±SEM	±2.7	±2.4	±8.9	±5.3	±3.9	±3.8	±2.8	±2.9	±1.0	±1.1	±2.9	±3.1
p	NS		NS		NS		<0.001		<0.01		<0.01	

BP = systolic blood pressure; HR = heart rate; NS = not significant; SEM = standard error of the mean; TT = treadmill time; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen consumption.

regurgitation or subpulmonic obstruction, and 2 had slightly diminished right ventricular contractility.

The 4 patients with TF had undergone repair, 2 with a transanular right ventricular outflow tract patch, 2 to 8.5 years earlier (mean 4.4) at a mean age of 39 months. One patient required reoperation for residual right ventricular outflow tract obstruction and pacemaker placement. Follow-up catheterization data were available in 3 patients. All patients had a normal cardiac index at rest, normal right and left ventricular end-diastolic pressures, and mildly elevated right ventricular systolic pressure (Table I). Angiographically, all had qualitatively normal right and left ventricular contractility. One patient each had mild, moderate and severe pulmonary insufficiency. All 4 patients had right bundle branch block.

Graded treadmill tests were conducted before and after 12 weeks of aerobic training. Tests were performed on a motor-driven treadmill (model 18-54, Quinton Instruments) while an electrocardiogram, cuff blood pressure and intermittent oxygen consumption were monitored. A modified Bruce protocol was used. Subjects were fitted with a mouthpiece containing a 2-way valve and a pneumotachograph (Fleish type, Dynasciences). Expired air was analyzed for oxygen and carbon dioxide content (Perkin-Elmer 1100 Medical gas analyzer). The outputs were sampled every 2 minutes for 30 seconds by a microcomputer (NOVA 3, Data General) programmed to assess and print minute ventilation, oxygen consumption and respiratory quotient. The subjects were encouraged to continue as long as possible to obtain maximal treadmill times. All tests were terminated owing to fatigue.

Training sessions were held in the gymnasium at Children's Hospital National Medical Center twice a week for 12 weeks. Each class was directed by an elementary physical education specialist with an exercise physiologist and pediatric cardiologist present. A portable defibrillator and an emergency medical cart were available in the room. Each class commenced with a 15-minute warm up period of stretching and flexibility exercises. Aerobic activities such as walking, running, jumping rope and modified aerobic dance followed the warm-up period and lasted 15 to 30 minutes. Workloads of 60%, 70% and 80% of maximal heart rate were achieved. Each session concluded with a 15 minute cool-down period to prevent venous pooling in the extremities. Rest, peak exercise and recovery single-lead electrocardiograms were recorded in all patients at each session with a portable device (MSG-IM Schiller). Starting in the sixth week of the program, all patients were instructed to spend at least 25 to 35 minutes once a week in home-based, family-oriented aerobic exercise (i.e., brisk walking or jogging).

Data analyzed for statistical significance included weight, heart rate, minute ventilation, peak systolic blood pressure, treadmill time and oxygen consumption. Measurements before and after training were compared by a Student paired t test. A p value <0.05 was considered significant. Electrocardiographic tracings were reviewed for rhythm disturbances and ST-T-wave changes.

Table II contains the exercise data of each patient before and after completion of the cardiac rehabilitation program. Maximal values are listed. Weight, heart rate and minute ventilation did not change significantly during the study

interval. Peak systolic blood pressure increased 17% (from 116 to 140 mm Hg, $p < 0.001$), treadmill time increased 18% (from 11.7 to 14.2 minutes, $p < 0.01$) and oxygen consumption increased 20% (from 37 to 45 ml/kg/min, $p < 0.01$). Treadmill electrocardiograms before and after the cardiac rehabilitation program did not document significant ST depression at peak exercise in any patient. Three of the 4 children with pacemakers had paced rhythm at rest; all 3 demonstrated sinus rhythm with peak exercise. There were no complications.

Conditioning programs for normal children have variable design, duration and intensity and produce improved levels of aerobic fitness as measured by maximal work capacity or maximal oxygen consumption.[2,9] The cardiopulmonary alterations that occur in normal school-aged children after a season of competitive swimming have been documented.[10] Only Goldberg et al[1] and Ruttenberg et al[2] studied the effects of exercise training on children after cardiac surgery. In the former study, a significant improvement in maximal work capacity occurred in patients with postoperative TF and ventricular septal defect. Maximal oxygen consumption did not significantly increase. Similarly, the study by Ruttenberg et al revealed significant improvement in maximal treadmill performance (time and stage) in patients with postoperative TF, aortic stenosis, TGA and arterioventricular canal, although maximal oxygen consumption did not change.

This study differs from those previously reported. The patients are younger than those studied by Goldberg and Ruttenberg and their co-workers and have more severe residual disease. Sixty percent of the study patients with TGA are pacemaker-dependent at rest. The mean systolic gradient across the right ventricular outflow tract in the TF group is 20 mm Hg. The duration of the training program is longer than that in either of the previous 2 studies. Because the program is hospital-based, electrocardiographic monitoring is possible. We confirmed that all participants exercised to achieve and maintain heart rates of 60 to 80% of maximum heart rate, which constitutes more intense exertion than in the study of Goldberg et al.

The current results, however, agree with those previously published. After training, heart rate and minute ventilation did not significantly change. Both peak systolic blood pressure and treadmill time improved substantially. In our patients maximal oxygen consumption also increased significantly, a result we attribute to the documented major increase in intensity and duration of our rehabilitation program.

A monitored pediatric cardiac rehabilitation program can improve the aerobic fitness of young children, even in the presence of moderate hemodynamic or electrophysiologic disturbance.

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Coarctation of the Aorta Inherited as an Autosomal Dominant Trait

ROBERT H. BEEKMAN, MD
MEINHARD ROBINOW, MD

Coarctation of the aorta (CoA) usually occurs sporadically.[1,2] Familial recurrence of CoA has been reported in sibling and parent-child groups, however, in patterns compatible with multifactorial inheritance.[2,3] In this report we describe a family in which CoA affected 4 generations in a pattern consistent with autosomal dominant inheritance. This is the first reported instance of CoA inherited in classic Mendelian fashion.

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***Case 1* (*IV 1, Fig. 1*):** *The index case presented at age 1 year for evaluation of a heart murmur. He was asymptomatic. Systolic blood pressure (Doppler) was 122 mm Hg in the right arm and 110 mm Hg in the legs. A grade 2/6 systolic ejection murmur was heard in the back. Cardiac catheterization revealed mild thoracic CoA, with a systolic gradient at rest of 10 mm Hg. No other cardiovascular abnormalities were present.*

***Case 2* (*III 7, Fig. 1*):** *This 29-year-old woman, in excellent health, was evaluated because of the striking family history of CoA. Her physical examination was unremarkable. Blood pressures at rest were 131/85 mm Hg in both arms and 132 mm Hg in the leg. A graded exercise test was performed in an attempt to elicit evidence of a subclinical CoA. Although no pressure gradient was present between arm and leg at rest, a 46-mm Hg systolic gradient was measured on multiple recordings immediately after peak exercise. Typical postexercise pressures were 148/50 mm Hg in the right arm and 102 mm Hg in the leg. An aortogram failed to document a CoA. No pressure gradient at rest was detected within any portion of the aorta.*

***Case 3* (*II 3, Fig. 1*):** *At age 15 years the patient had a blood pressure of 240/100 mm Hg in the right arm and 120/80 mm Hg in the leg. Murmurs consistent with aortic stenosis*

and insufficiency were present. A chest radiograph showed severe cardiac enlargement and rib notching. Surgical repair of the CoA was performed by excision and end-to-end anastomosis. Although the pressure gradient at rest was abolished, persistent hypertension and aortic insufficiency led to the patient's death 7 years later at age 22 years.

Case 4 (II 2, Fig. 1): *The patient developed hypertension, dyspnea on exertion and frequent headaches in her teens. At age 28 years, after 3 syncopal episodes, she was found to have a blood pressure of 200/120 mm Hg in the arms and diminished femoral pulses. At surgery, a tight thoracic CoA was repaired by excision and end-to-end anastomosis. On the first postoperative day the patient had a cardiac arrest and died.*

Case 5 (I 1, Fig. 1): *Upper extremity hypertension was first discovered when this women was 25 years old. She was treated medically and followed a satisfactory course until age 68 years, when she was hospitalized with chest pain and supraventricular tachycardia. Blood pressure was 220/120 mm Hg in the arms and 90 mm Hg in the legs. Soon after admission ventricular fibrillation developed and she died. Necropsy revealed severe thoracic CoA and multiple large collateral vessels.*

Other relatives: *No other members of the family have been studied. Members I 1 and I 2 (Fig. 1) are in good health in their late 70s and are presumably unaffected.*

Familial coarctation of the aorta is rare.[1,2] Only 26 families have been reported previously in which CoA occurred in more than 1 member.[1–5] In no family has CoA affected more than 2 generations, and in no instance has a pattern of Mendelian inheritance appeared. Familial CoA, as with most other types of congenital heart disease, has been attributed to multifactorial causation.[2,3] In the present report a family is described in which CoA appears to have been transmitted as an autosomal dominant trait with high penetrance and variable expressivity. Five family members in 4 generations have been affected, some with severe and others with mild CoA. (X-linked dominant inheritance cannot be ruled out because there has been no male-to-male transmission.) Case 2 appears to be a carrier, since her aorta was not grossly abnormal by angiography. The exercise-induced pressure gradient in this patient is difficult to explain, however, as one does not occur in normal persons.[6] It is tempting to speculate that this patient has a minimal expression of the trait in which a segment of aorta, although not anatomically narrowed, lacks the compliance to dilate normally during exercise.

The concept that genetic factors influence the development of CoA in some patients is not new. It is well known, for instance, that CoA occurs commonly in patients with XO Turner syndrome. Classic Mendelian inheritance of CoA, however, has not been previously documented. In this report we have described a family in which CoA was traced through 4 generations in a pattern consistent with autosomal dominant inheritance.

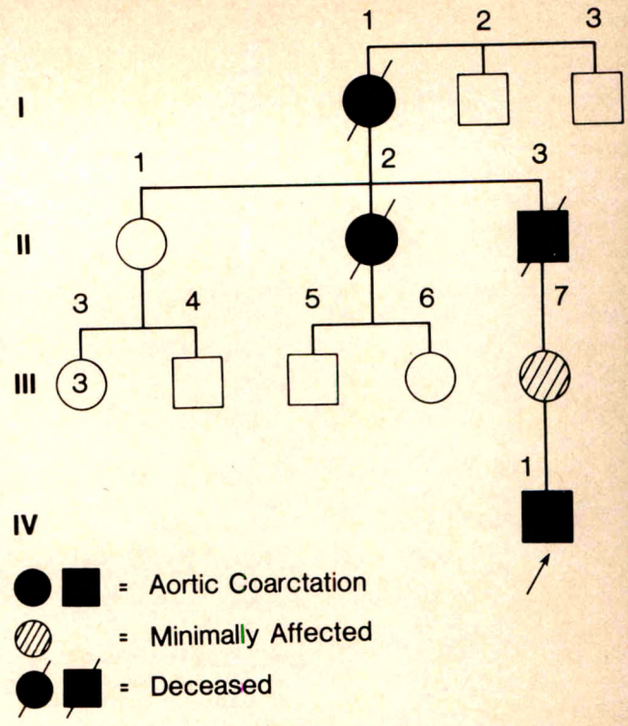

FIGURE 1. Family pedigree showing the recurrence of coarctation of the aorta in 4 generations.

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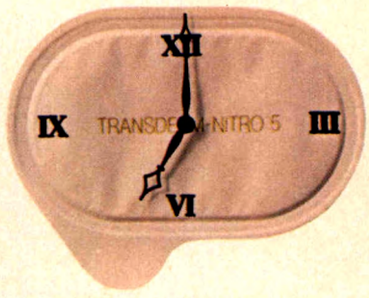

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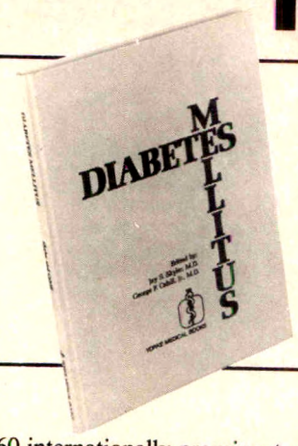

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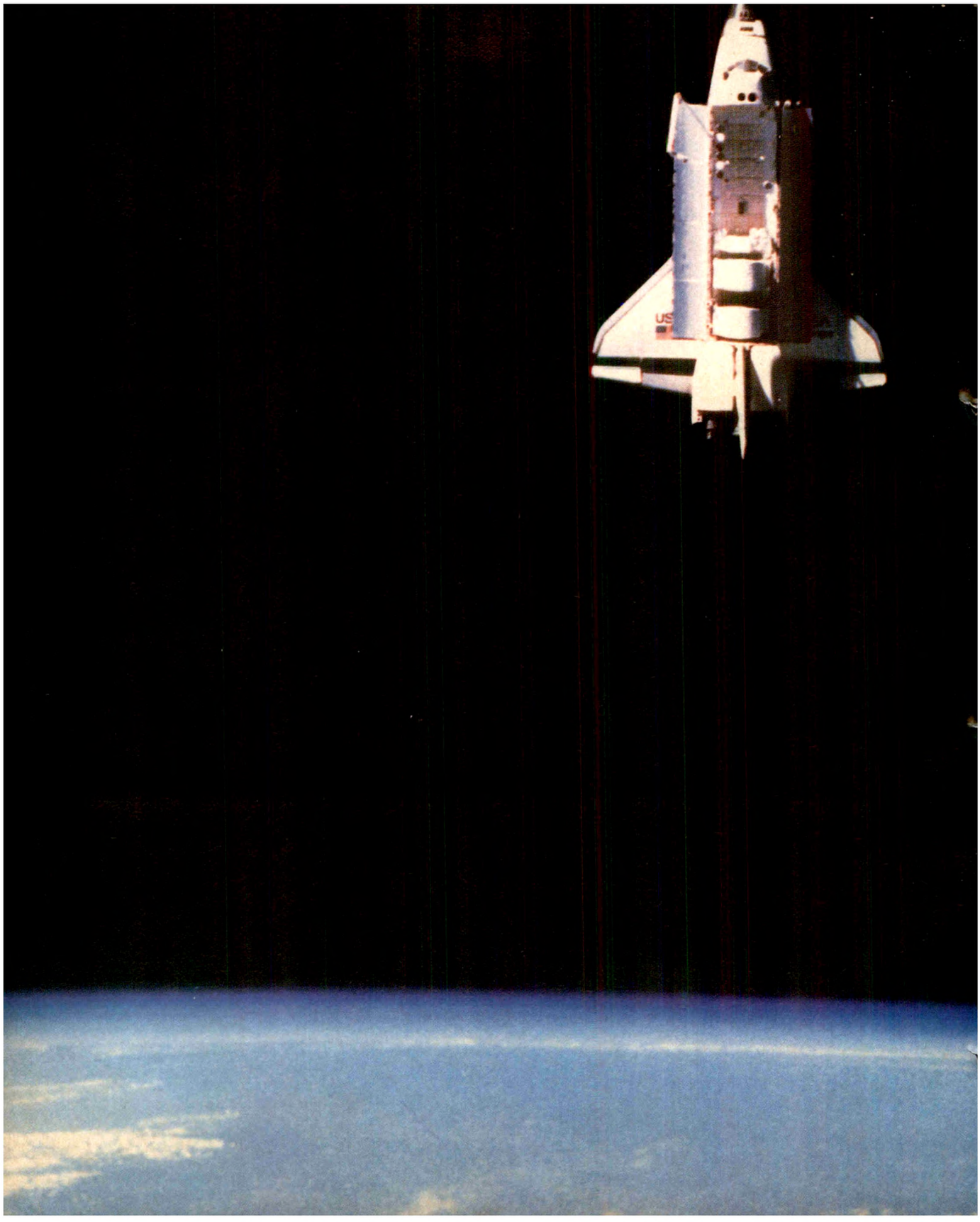

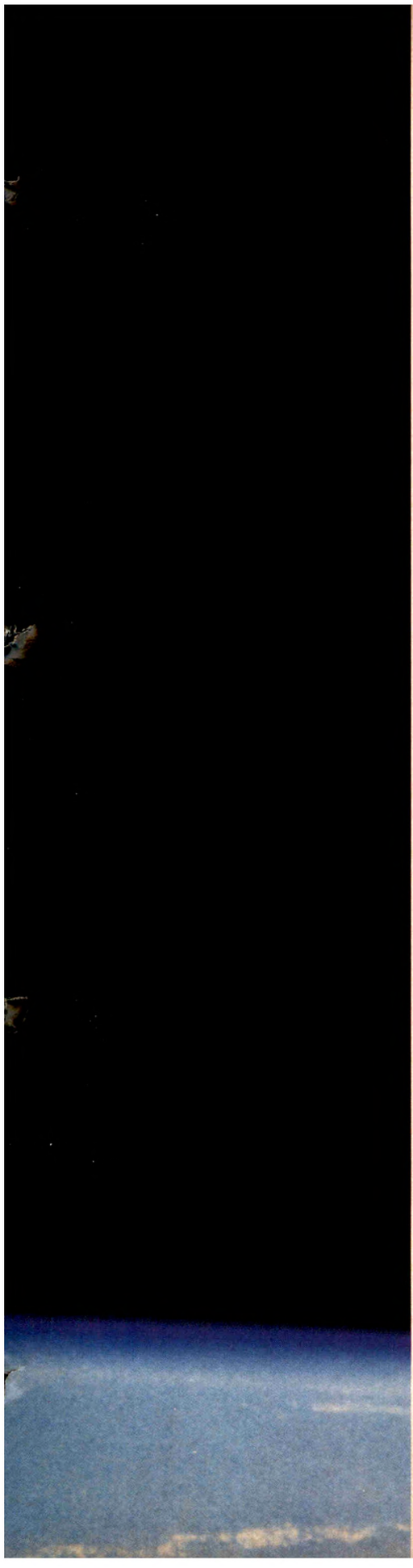

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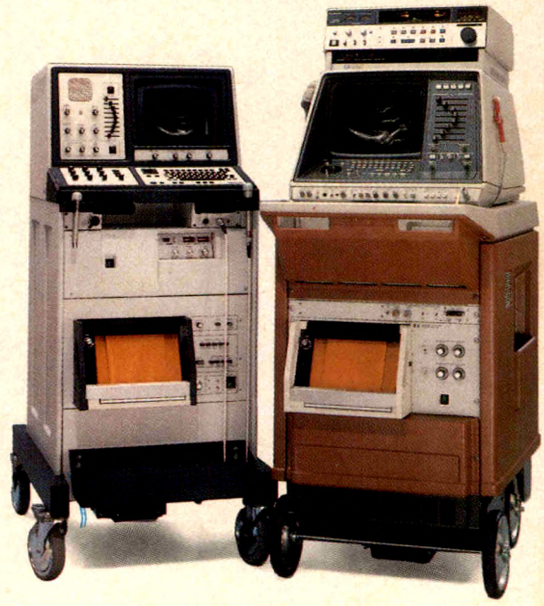

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Please see last page for brief summary, including warnings, precautions, and adverse reactions.

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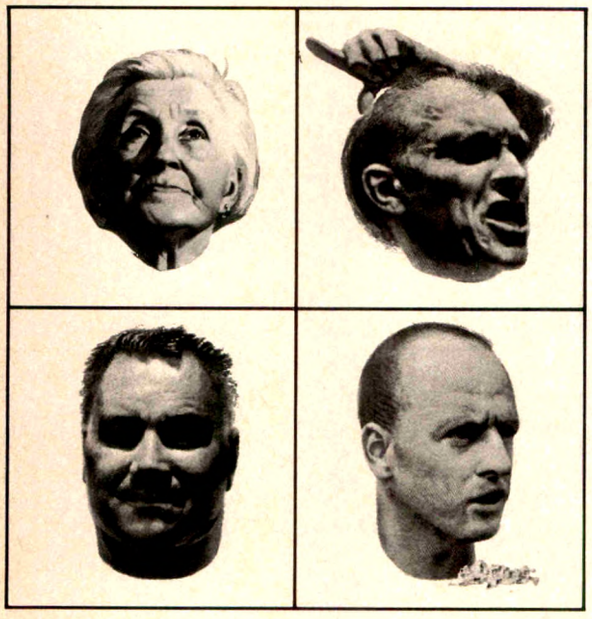

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Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.

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Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000 and unit dose package of 100. Also available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.
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Reference:

1. Pioneering Research in Hypertension: The Role of the Sympathetic Nervous System, film and monograph, Boehringer Ingelheim Ltd., 1982.

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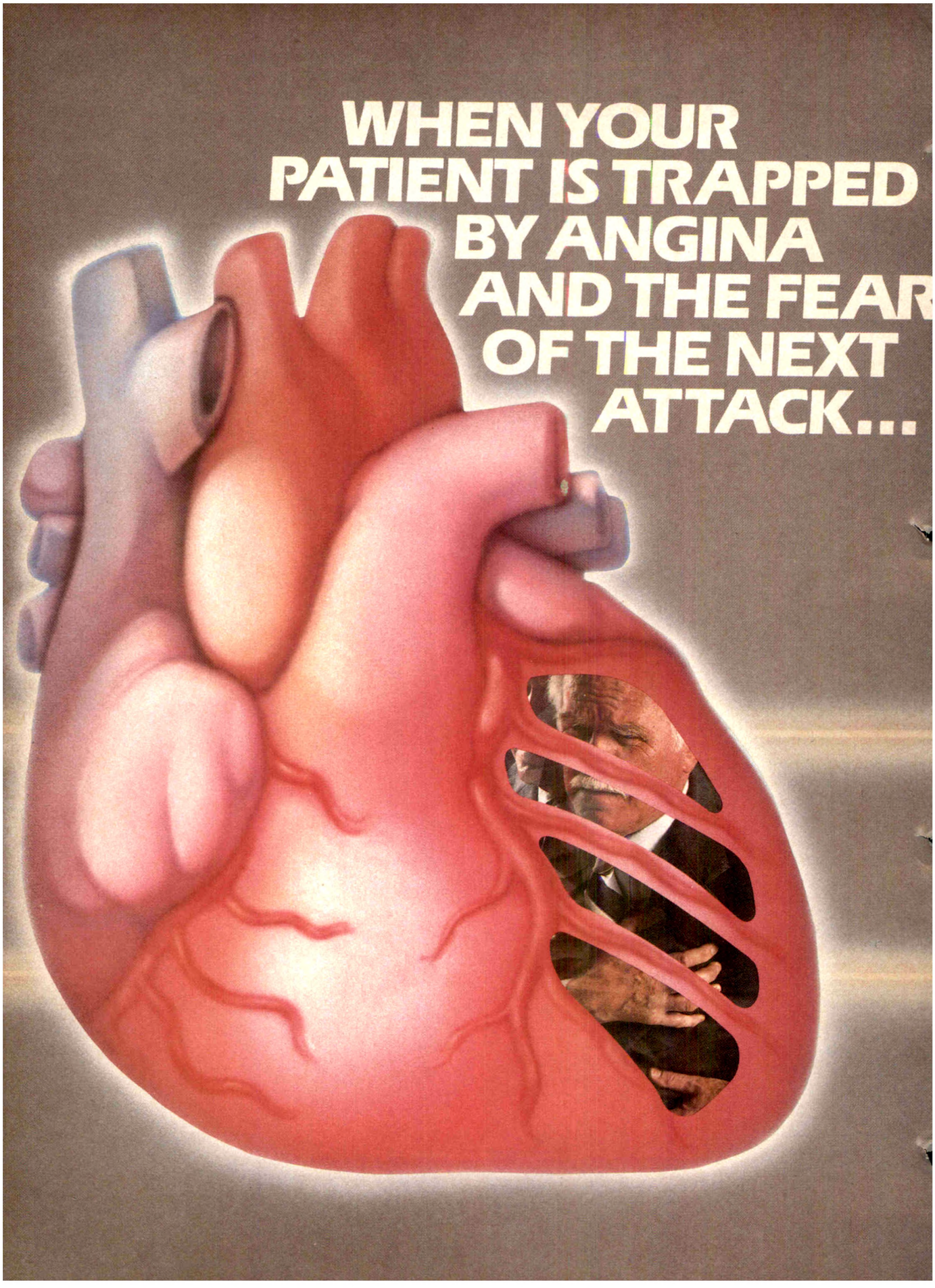
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AND THE FEAR
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*The syndrome of recurring symptoms compounded by the fear of impending attacks.

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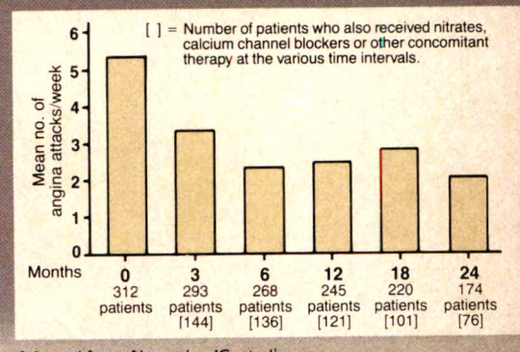
In a two-year study, CORGARD reduced the frequency of attacks from 5.3 per week to 2.1.[1]



Adapted from Alexander JC, et al[1]

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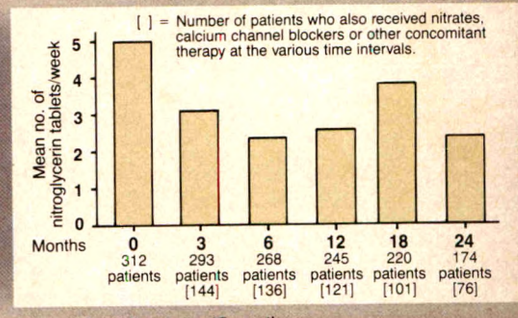
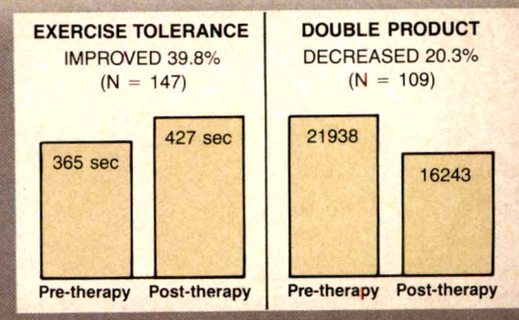


Adapted from Alexander JC, et al[1]

IMPROVES EXERCISE TOLERANCE

CORGARD significantly increases the patient's ability to participate in physical activity.[2]



References: 1. Alexander JC, et al: Long-term experience with nadolol in treatment of hypertension and angina pectoris. Am Heart J 108:1136-1140, 1984. 2. Data on file, Squibb Institute for Medical Research.

Please see brief summary of prescribing information on adjacent page.

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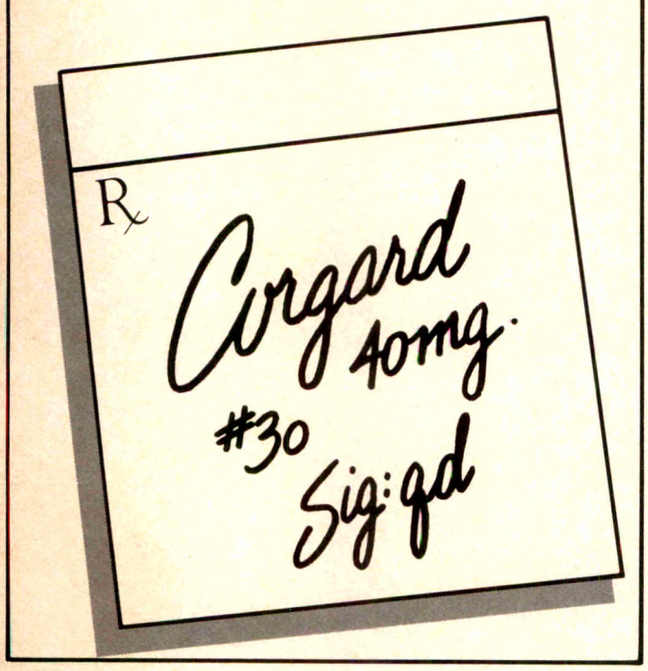

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy—In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia. The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There *is* evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

References: 1. Alexander JC, et al: Long-term experience with nadolol in the treatment of hypertension and angina pectoris. Am Heart J October Supplement 108 (4):1136-1140, 1984. 2. Data on file, Squibb Institute for Medical Research.

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Two-Dimensional Echocardiographic Diagnosis of Total Anomalous Pulmonary Venous Connection Below the Diaphragm

PUI-KAN LIAO, MD
WEN-JEN SU, MD
JUI-SUNG HUNG, MD

In cyanotic neonates, the presence of total anomalous pulmonary venous connection (TAPVC) often mimics pulmonary parenchymal disease, persistent fetal circulation and many other forms of cyanotic congenital cardiac malformations. In the last group with cardiac malformations, abnormalities of great arteries and intracardiac structures are readily identified by 2-dimensional echocardiography (2-D echo). When 2-D echo with contrast medium reveals normal intracardiac anatomy and a right-to-left atrial or ductal shunt, differentiation of TAPVC from pulmonary parenchymal disease and persistent fetal circulation remains a problem. Although characteristic features of TAPVC in 2-D echo have been described, experience in application of this diagnostic tool to the infradiaphragmatic type of TAPVC is limited.[1–4] We report 2-D echocardiographic findings of 2 neonates with infradiaphragmatic TAPVC.

Two-dimensional echo was performed in 2 cyanotic neonates with respiratory distress, aged 33 days (patient 1) and 2 days (patient 2), respectively. The diagnosis of infradiaphragmatic TAPVC was confirmed by angiography and at operation in patient 1. Patient 2 died a few hours after the echocardiographic examination before cardiac catheterization was performed.

The patients were examined in the supine position with the transducer placed in the precordial, subcostal and suprasternal positions. Standard echocardiographic views as described by Tajik et al[5] were obtained to assess the cardiac chambers, septa, cardiac valves, great arteries, great veins and the abdominal visceral situs. A Hewlett-Packard phased-array ultrasound system and an Aloca SSD 710 mechanical sector scanner, both with a 5-MHz focused transducer, were used in each case, respectively.

Two-dimensional echo in both patients showed normal ventricular and great artery anatomy with dilated right-sided heart chambers and the main pulmonary artery. The pulmonary valve showed typical motion of pulmonary hypertension on the M-mode display. An ostium secundum–type atrial septal defect and large patent ductus arteriosus were demonstrated in each case. The most striking finding in these 2 patients consisted of an enormously dilated venous channel, which ran posteroanteriorly in the craniocaudal direction within the liver on the longitudinal cut of the upper abdomen (Fig. 1A and 2A). It could easily be distinguished from the descending abdominal aorta and the normal-sized inferior vena cava (Fig. 1B and 2B). On the short-axis cut of the upper abdomen, this abnormal venous channel was located anterior to the inferior vena cava and the descending aorta near the midline but slightly to the left or right of the spine (Fig. 1C and 2C). Multiple communication between the abnormal venous channel and the intrahepatic veins (presumably portal veins) was demonstrated. The abnormal vein showed no direct connection with the inferior vena cava.

Despite presence of a small pulmonary vein-like structure joining the left atrium near the atrial septum in the subcostal view, no other pulmonary veins could be found. In view of these findings, infradiaphragmatic TAPVC was diagnosed.

Diagnosis of TAPVC by 2-D echo depends on demonstration of absence of normal pulmonary venous connection to the left atrium, presence of a common pulmonary vein, and the exact mode of abnormal connection of the common pulmonary vein.[1–4] In each of our patients, the diagnosis of infradiaphragmatic TAPVC was made because these criteria were satisfied.

From the Department of Pediatrics and the Department of Medicine, Chang Gung Memorial Hospital, 199 Tung Hwa North Road, Taipei 105, Taiwan, Republic of China. Manuscript received March 19, 1985; revised manuscript received May 6, 1985, accepted May 7, 1985.

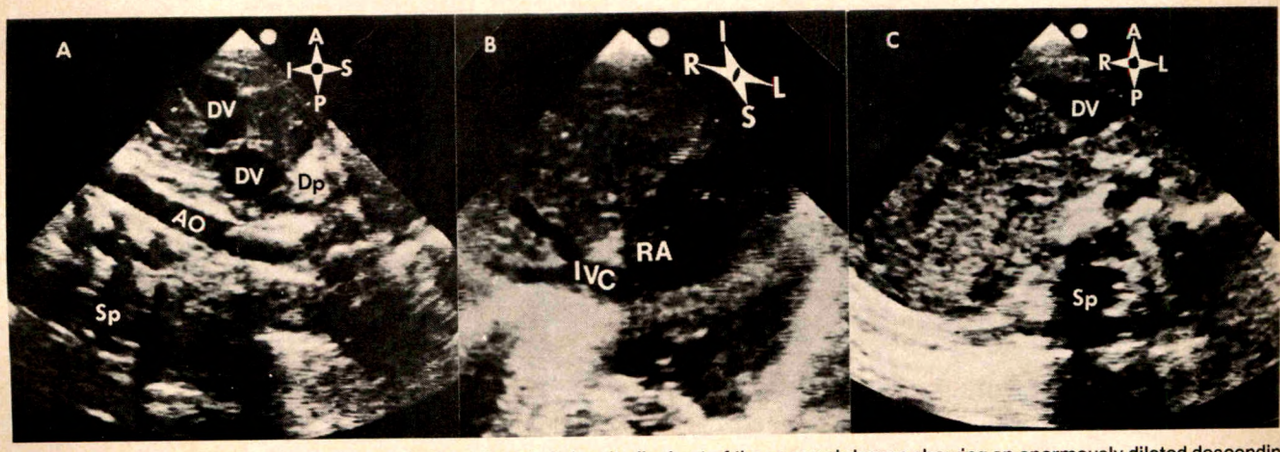

FIGURE 1. Two-dimensional echocardiogram from patient 1. **A,** longitudinal cut of the upper abdomen showing an enormously dilated descending vein (DV) in the liver. **B,** subcostal 4-chamber view showing the normal-sized inferior vena cava (IVC). **C,** short-axis cut of the upper abdomen showing communication of the descending vein with the portal veins. A = anterior; AO = descending aorta; Dp = diaphragm; I = inferior; L = left; P = posterior; PV = portal vein; R = right; RA = right atrium; S = superior; Sp = spine.

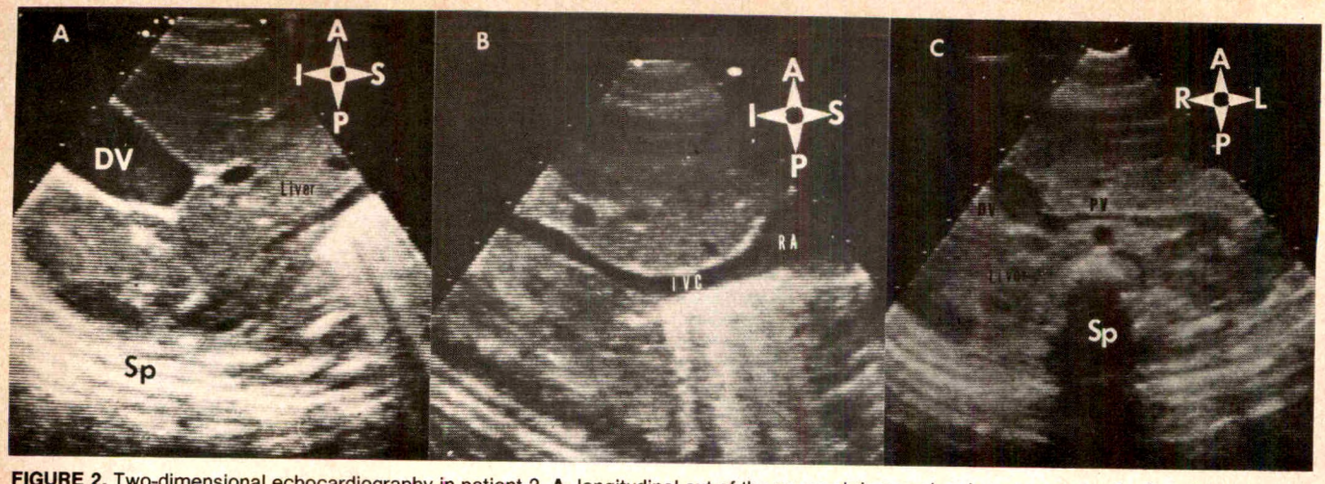

FIGURE 2. Two-dimensional echocardiography in patient 2. **A,** longitudinal cut of the upper abdomen showing an enormously dilated descending vein in the liver. **B,** normal-sized inferior vena cava draining into the right atrium. **C,** short-axis cut of the upper abdomen showing communication of the descending vein with the portal veins. Abbreviations as in Figure 1.

In 1 patient the diagnosis was further confirmed at operation.

Normal pulmonary venous connection to the left atrium can usually be identified by 2-D echo in 3 views: apical, subcostal and suprasternal.[1,3,5] However, failure in demonstrating pulmonary venous connection to the left atrium cannot by itself be construed as evidence for abnormal pulmonary venous drainage. Hence, demonstration of a dilated common pulmonary vein, usually behind the left atrium, is of paramount importance in the diagnosis of TAPVC. To achieve this, proper gain settings and careful scanning of the pulmonary veins in different echo planes by apical, subcostal and suprasternal approaches are mandatory, lest a diagnosis of normal pulmonary venous drainage be falsely made. This is exemplified in our experience with both patients. When examined initially from the subcostal position, we had a false impression of normal connection of the right upper pulmonary vein with the left atrium. Visualization of a dilated descending common pulmonary vein in the liver with subsequent scanning provided a clue for the diagnosis of TAPVC. The small, alleged pulmonary vein most likely represented 1 of the horizontal veins behind the left atrium just above the diaphragm. False connection of this pulmonary vein with the left atrium probably resulted from poor image resolution in this particular subcostal view. In a deeper subcostal cut of the long axis of the 2 atria, a mildly dilated pulmonary venous confluence, clearly separated from the left atrium, was demonstrated.

Acknowledgment: We thank Hsin Leen Tao and Grace T.C. Tsai for their secretarial assistance.

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Computerized Tomography and Ultrasound in the Noninvasive Evaluation of Coarctation of the Aorta

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Two-dimensional echocardiography (2-D echo) is helpful in evaluating anomalies of the aortic arch in newborns, but has several limitations in adults.[1] We examined the role of computerized tomography (CT) together with 2-D echo and continuous-wave (CW) Doppler scanning in the noninvasive evaluation of aortic coarctation.

During the last 6 months we observed 5 patients, aged 8 to 54 years, with coarctation of the aorta confirmed by angiography. Three of them underwent surgery for elective repair by the subclavian flap technique. Two-dimensional echo was performed using a Diasonics 3400 R with a 2.5-MHz, phased-array transducer. A view of the aortic arch was obtained from the upper left sternal border and suprasternal notch. A continuous-wave Doppler echocardiogram was recorded with a Irex-Pedoff system, with a 2-MHz ultrasonic frequency; the transducer was placed in the suprasternal

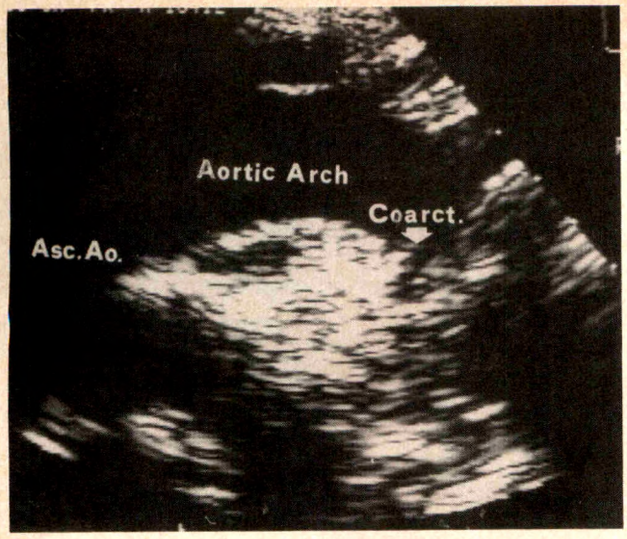

FIGURE 1. Two-dimensional echocardiographic image from the suprasternal notch of the ascending aorta (Asc. Ao.), aortic arch and descending aorta. The level of coarctation (Coarct, **arrow**) is shown.

notch in the first or second left intercostal space, with the probe directed toward the descending aorta. In the position in which the highest frequencies could be heard, peak velocity together with spectral analysis of the Doppler signal and electrocardiogram were recorded. As described previously,[2] maximal velocity across the obstruction can be used to calculate the pressure drop across the obstruction from the modified Bernoulli formula: $p^1 - p^2 = 4v^2$, where v is maximal velocity in the jet and p^1 and p^2 are the pre- and postobstruction pressures. The CT examination was done with a General Electric 9800 system using very short scan times (1.3 seconds, partial scan, 2 seconds) and high-contrast resolution (image reconstruction 512 × 512). Multiple CT scans were obtained during the infusion of 150 ml of contrast

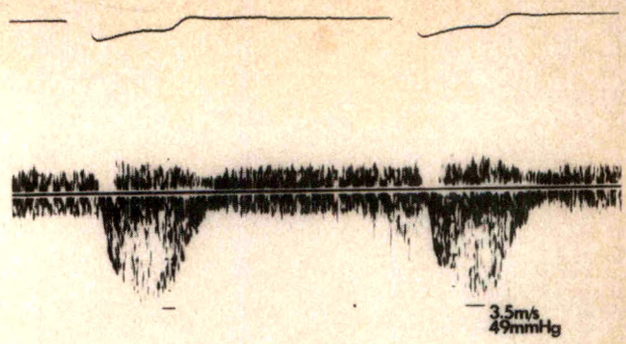

FIGURE 2. Continuous-wave Doppler recording of the maximal velocity flow obtained in the descending aorta after the obstruction. The gradient is derived from peak velocity.

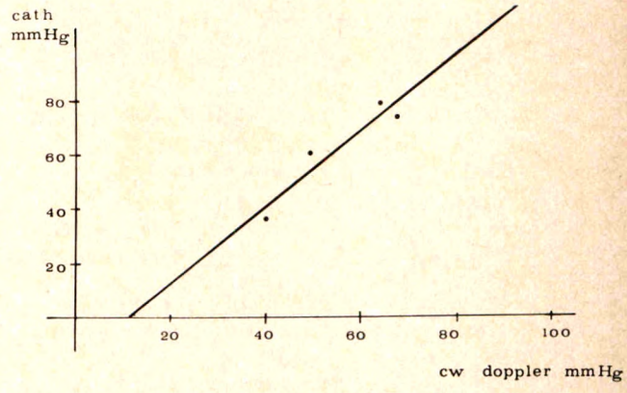

FIGURE 3. Relation between the systolic gradient obtained at catheterization and the pressure drop predicted by using simplified Bernoulli equation and continuous-wave (CW) Doppler (r = 0.94).

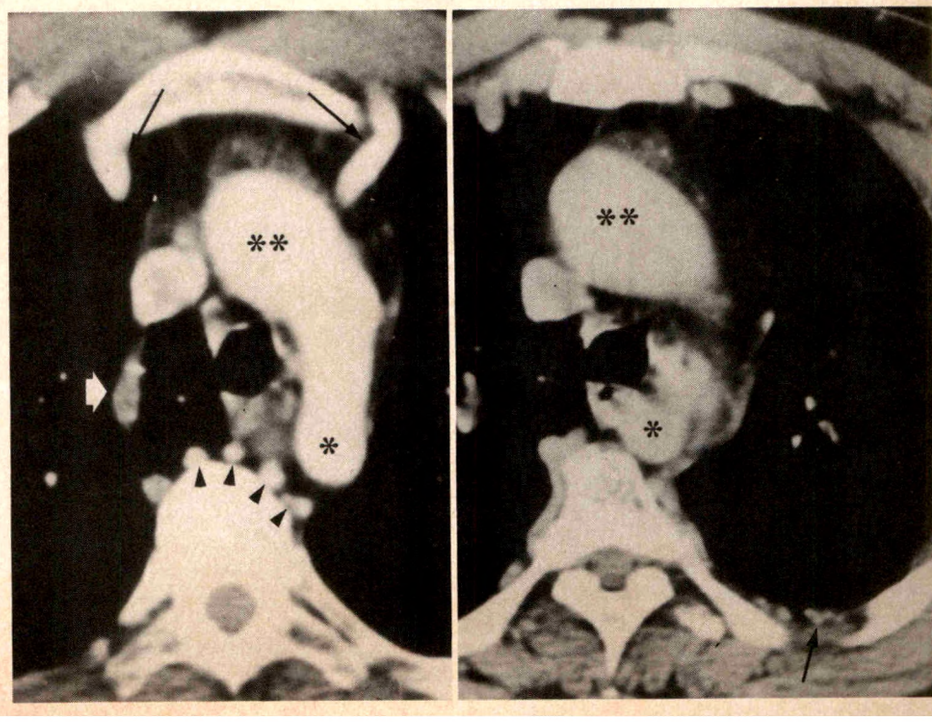

FIGURE 4. Left, computerized tomographic (CT) scan through the aortic arch. The difference in size between ascending (**) and descending (*) aorta is conspicuous. Ectasia of both internal mammary arteries (**black arrows**) are visible. Crown-like collateral circles can be seen in front of the vertebral body (**arrowheads**). The anomalous course of azygos vein (**white arrow**) is shown. **Right,** CT scan at the level of the aortopulmonary window. The difference in size between ascending (**) and descending (*) aorta is even more conspicuous. Intercostal collateral circles responsible for rib notches are quite visible (**arrow**).

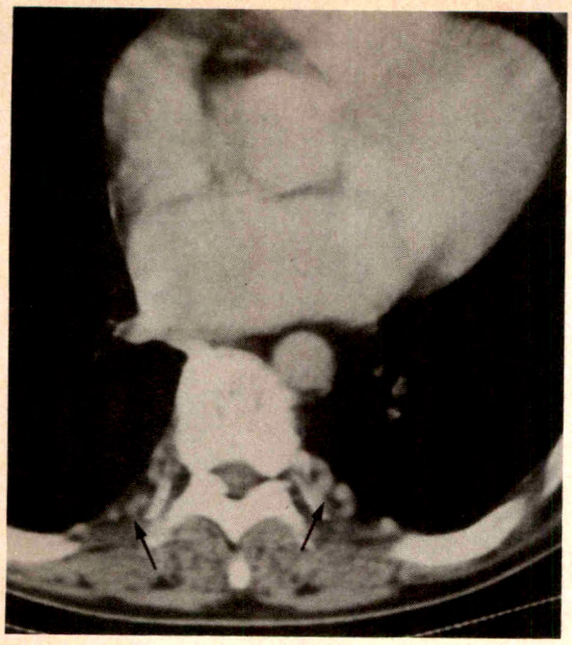

FIGURE 5. Computerized tomographic scan at the level of the left atrium. Paraspinal collateral circles are bilateraly visible (**arrows**).

medium from the thoracic inlet to the diaphragm. More scans were taken with less slice spacing and thickness in the aortic region. Sagittal, coronal and oblique reformatted CT images were also obtained. To better define the vascular structures of the chest wall, dynamic scanning at the tracheal bifurcation level was done with rapid injection of 40 ml of contrast medium. To confirm the previous data, pressure measurements and an aortogram were obtained in each patient under local anesthesia.

Two-dimensional echo evidence of coarctation was clear enough for diagnosis in only 2 patients (Fig. 1) because of technical problems in the suprasternal approach. By CW Doppler a high velocity jet from beyond the coarctation was recorded in 4 patients (Fig. 2) and the pressure drop was measured. Figure 3 shows the good correlation (r = 0.94) between peak pressure drop using CW Doppler and catheterization data.

CT scans (Fig. 4 and 5) provided 3 main types of information in all patients. These were: the shape and size of prestenotic and poststenotic aorta and great vessels; the amount of collateral circulation, which usually develops through the subclavian arteries (internal thoracic, transverse scapular) and intercostal arteries, the vertebral arteries and anterior spinal arteries; and the detection of other possible associated vascular anomalies.

It is well known[3] that angiography is the ideal instrument for the diagnosis and the surgical approach of aortic coarctation. Nevertheless, there are other noninvasive techniques that can be extremely useful in the definition of this malformation.[1] In the general population, chest x-rays can suggest the presence of aortic coarctation.[3] It is possible to recognize the "figure of 3" sign directly, or indirectly by the barium-filled esophagus. The frequency of visible rib notching correlates directly with age and inversely with the diameter of the coarctation measured in the resected specimen.[4] Glandy et al[4] reported that chest film reveals aortic coarctation in 66% of patients. In our experience CT was much more useful for the direct visualization and anatomic definition of all the different collateral roots. CT, sometimes together with 2-D echo, can anatomically determine the side and size of the obstruction. Although 2-D echo presents several technical problems in adults, it was nevertheless useful for the diagnosis of the bicuspid aortic valve, which is present in 85% of patients.[5] The big gap between traditional hemodynamic evaluation and noninvasive techniques has been overcome by CW Doppler, which provides pressure drop values. Recently Wyse et al[6] have reported that a high correlation (r = 0.85) was present between CW Doppler data and the arm-to-leg systolic blood pressure difference in 30 children affected by coarctation. In our experience CW Doppler presented a better correlation (r = 0.94) with the invasive data.

Acknowledgment: We thank Germana Sitta, Maria Pia Ferrari and Maria Angela Dondi for secretarial and technical assistance and Mauro Giovanardi for preparing the illustrations.

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Arrhythmias and Left Ventricular Function in Chronic Alcoholics with Alcoholic Cirrhosis

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Arrhythmias have been reported to occur in chronic alcoholics both as a secondary phenomenon to an overt cardiomyopathy[1] or as a primary event in absence of myocardial dysfunction.[2] Alcoholics with normal cardiac function may have severe arrhythmias after acute alcohol ingestion with return to normal rhythm during abstinence.[3] Because depression of myocardial function and arrhythmias occur both in animals and man[4] after acute alcohol consumption, the relation between ventricular dysfunction and arrhythmias in chronic alcoholism is difficult to establish. The role of alcohol in the onset of arrhythmias in chronic alcoholics with no episodes of acute ingestion and without overt alcoholic cardiomyopathy is also difficult to investigate because apparently healthy subjects may have arrhythmias.[5] We analyzed the arrhythmias and their relation to left ventricular (LV) function in a selected group of asymptomatic alcoholic patients with alcoholic cirrhosis and compared the findings with those from healthy nonalcoholic subjects.

Between April 1984 and September 1984, 12 chronic alcoholics, 7 men and 5 women, were studied at the Department of Medicine of Padua Medical Center. The patients' mean age was 37 years (range 30 to 45) and the criteria for admission in the study group were: consumption of 160 g/day of ethanol for at least 5 years; no evidence of congenital or acquired heart disease, lung disease, hypertension or diabetes; no therapy with cardiac medication or antiarrhythmic drugs; results of physical examination, electrocardiography and chest x-rays within normal limits; age younger than 45 years; and histologically ascertained hepatic damage (chronic alcoholic hepatitis in 6 patients and alcoholic cirrhosis in the remaining 6).

Twenty-four-hour Holter electrocardiograms, systolic time intervals and M-mode echocardiograms were recorded in each subject after 6 to 10 days (mean 7) of abstinence. On the day of Holter recording, serum potassium, calcium and (in 7 patients) magnesium levels were measured. Potassium and calcium levels were borderline, decreased or normal. The magnesium levels were slightly decreased in 2 alcoholic patients.

An age-matched control group of 10 nonalcoholic subjects (6 men and 4 women), selected among physicians and nurses of our department, underwent the same investigation except for the liver biopsy. Criteria of inclusion in the control group were absence of history of cardiovascular disease or symptoms and results of physical examination, electrocardiography and chest x-rays within normal limits.

Qualitative ventricular ectopy was described as uncomplicated (unifocal or uniform ventricular complex) and complicated (multiform or multifocal ventricular complexes, couplets, 3 or more consecutive ventricular premature beats and R-on-T phenomenon). Quantitative ventricular premature beats were classified as: not frequent (less than 30 beats/hour) and frequent (more than 30 beats/hour).

In the alcoholic group, 1,345 ventricular premature complexes and 41 supraventricular ectopies were found (Table I). Ventricular arrhythmias occurred in 5 of 12 patients (42%). The only patient of these 5 with frequent ventricular premature complexes also had complex arrhythmias, whereas the other 4 had occasional and simple ventricular premature complexes (Fig. 1). In the control group, 27 supraventricular and 1,234 ventricular complexes were detected (Table I). Only 3 patients (30%) in this group had arrhythmias: 2 had simple and occasional arrhythmias and only 1 patient had complex and frequent arrhythmias.

The mean value of echocardiographic indexes (shortening fraction, ejection fraction, LV diastolic thickness to radius ratio[6]) was normal and there was no significant difference in the 2 groups (Table II). The preejection period (PEP) corrected for heart rate according to the method of Weissler et al,[7] was significantly longer in alcoholics ($p < 0.05$) (Table III), but ejection time index was not different in the 2 groups. The PEP/LV ejection time ratio was slightly increased in alcoholics, but was not statistically significant ($p > 0.10$) (Table III).

The polygraphic and echocardiographic data were analyzed with the Student t test and F test. The comparison of the incidence of arrhythmias in the 2 groups was based on the χ^2 analysis with the Yates correction.

Our data suggest no difference in the rhythm disturbances occurring between chronic alcoholics without acute influence of alcohol and those found in normal persons. The distribution of arrhythmias was not sta-

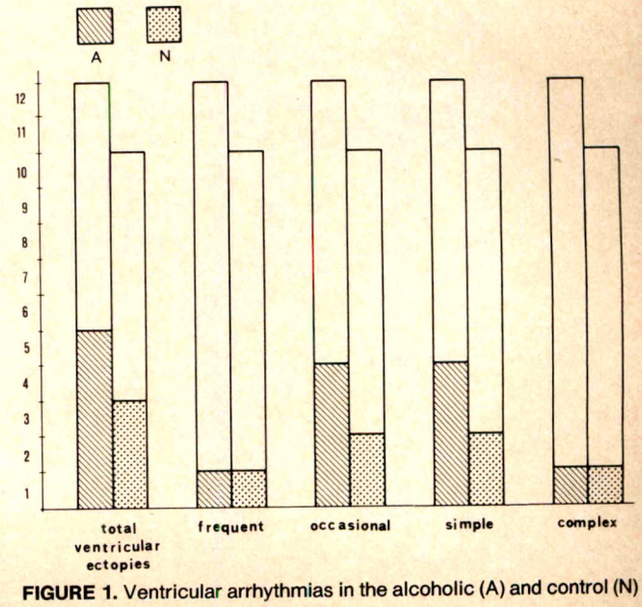

FIGURE 1. Ventricular arrhythmias in the alcoholic (A) and control (N) groups.

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TABLE I Arrhythmias Observed in Chronic Alcoholics and in Normal Subjects

	Arrhythmic Subjects	Arrhythmogenic Events	Premature Complexes	Ventricular Arrhythmias			
				Occasional	Frequent	Simple	Complex
A (n = 12)	10 (83%)	7 (57%) SVE 5 (42%) VE	SVE = 41 VE = 1,345	4 (33%)	1 (8%)	4 (33%)	1 (8%)
N (n = 10)	7 (70%)	6 (60%) SVE 3 (30%) VE	SVE = 27 VE = 1,234	2 (20%)	1 (10%)	2 (20%)	1 (10%)

A = alcoholics; N = normal subjects; SVE = supraventricular ectopies; VE = ventricular ectopies.

TABLE II Statistical Analysis on Echocardiographic Data

Parameters		Mean	Variance	SD	F Test	p	Student *t* Test	p
Dd	A	46.8	25.2	5.0	1.10	NS	0.62	0.70
	N	45.4	27.7	5.3				
Ds	A	29.4	11.2	3.3	1.24	NS	0.94	NS
	N	28.0	13.8	3.7				
LVWTd	A	10.9	2.9	1.7	2.26	NS	0.92	NS
	N	10.3	1.3	1.1				
SVT	A	9.8	1.2	1.1	1.08	NS	0.07	NS
	N	9.8	1.3	1.1				
Th/r	A	0.44	4.9E-03	0.07	1.00	NS	0.19	NS
	N	0.45	4.9E-03	0.07				
SF%	A	0.37	1.4E-03	0.04	1.17	NS	1.07	NS
	N	0.38	1.2E-03	0.03				
EF	A	0.62	1.5E-03	0.04	1.33	NS	0.63	NS
	N	0.63	2.0E-03	0.04				

A = alcoholics; Dd = diastolic diameter; Ds = systolic diameter; EF = ejection fraction; LVWTd = left ventricular diastolic thickness to radius; N = normal subjects; NS = not significant; SD = standard deviation; SF% = left ventricular percent fractional shortening; SVT = supraventricular tachycardia; Th/r = thickness to radius ratio.

TABLE III Statistical Analysis of Polygraphic Data

Parameters		Mean	Variance	SD	F Test	p	Student *t* Test	p
Age	A	37	27	5.2	2.21	NS	0.05	NS
	N	37	12	3.5				
HR	A	73	64	8.0	1.78	NS	0.19	NS
	N	72	114	10.7				
PEPI	A	132	248	15.8	1.92	NS	2.09	0.05
	N	119	129	11.4				
LVETI	A	423	142	11.9	1.09	NS	0.10	NS
	N	422	130	11.4				
PEP/LVET	A	0.33	2.9E-03	0.05	1.93	NS	1.42	NS
	N	0.30	1.5E-03	0.04				

A = alcoholics; HR = heart rate; LVETI = left ventricular ejection time index; N = normal subjects; NS = not significant; PEPI = preejection period index; SD = standard deviation.

tistically different ($p > 0.90$) in the 2 groups. Ventricular arrhythmias occurred in 5 alcoholics and in 3 healthy subjects, but frequent and complicated arrhythmias occurred in only 1 subject in each group. Our data are in agreement with those recently reported by Greenspon et al[3] and Zoneraich et al,[8] who showed that chronic alcoholics not under the influence of acute alcohol ingestion do not have significant arrhythmias.

Myocardial contractility (ejection and shortening fraction) were normal. In our series, the lack of any increase in wall thickness, considered by some investigators[6,9] as a sign of initial alcoholic cardiomyopathy, may be explained by the relatively younger age of our patients compared with others,[6,9] or possibly to a different kind of alcohol ingested. The population of English-speaking countries is more inclined to drink liqueurs rather than wine; wine is the most common alcoholic drink in the Mediterranean areas.

The discrepancy between the abnormality of systolic time intervals and the normal values of echocardiographic indexes has also been noted by Askanas et al.[10] They postulated decreased compliance of the hypertrophied left ventricle as the probable cause for the abnormal systolic time intervals. Our data do not appear to support his hypothesis, because in our patients the thickness of the left ventricle was not increased. In 2 alcoholic patients, the PEP index was clearly prolonged (154 ms), but neither patient had significant arrhyth-

mias. However, the only patient with complex and frequent arrhythmias also had a significant prolonged PEP index (147 ms).

Despite the small number of patients examined, our impression, based on the results obtained, is that the arrhythmogenic role of alcohol if not acutely ingested) is relatively unimportant. Our study confirms the finding that chronic alcoholics have an incidence of arrhythmias similar to normal subjects.

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Left Ventricular Thrombi in Association with Normal Left Ventricular Wall Motion in Patients with Malignancy

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The ability of 2-dimensional echocardiography to demonstrate intraventricular thrombi has stimulated interest in the natural history of thrombi and their potential to embolize.[1] Since most intraventricular thrombi occur in conjunction with regional wall motion abnormalities, their occasional association with normal ventricular motion and the possible role in systemic embolization in such patients has not been emphasized. We report left ventricular (LV) thrombi in 2 patients with normal LV wall motion who had embolic events.

Case 1: *A 43-year-old man with myelogenous leukemia, without a history of cardiac disease, was admitted with sudden onset of pain and numbness in both legs. Both legs were cold, pale and pulseless. Findings of cardiac examination were normal. The electrocardiogram was normal except for nonspecific T-wave abnormalities. The white cell count was 29,800 mm^3 with 21% eosinophils. Angiography confirmed embolic occlusion of both popliteal arteries. A Fogarty embolectomy was performed and large clots consisting of organizing thrombus with fibrin and red cells were recovered. An echocardiogram revealed normal cardiac valves and cardiac chambers. A large, mobile thrombus was noted within the left ventricle. LV wall motion was normal and the endocardium appeared normal (Fig. 1, A and B). Intravenous heparin administration was started. Several weeks later, embolic occlusion of the right femoral artery occurred, again requiring embolectomy. Repeat echocardiography revealed the thrombus to have decreased in size. Wall motion remained normal. The patient's recovery was uneventful and he was discharged on warfarin therapy.*

Case 2: *A 57-year-old woman with metastatic oat cell carcinoma of the right lung was admitted with a pathologic fracture of the right femur. There was no history of cardiovascular disease. Cardiovascular examination was normal. The hemoglobin was 8.7 g/dl. The white blood cell count was normal. The electrocardiogram showed nonspecific ST-T abnormalities. After surgery for the pathologic fracture, tachycardia developed. An echocardiogram revealed normal LV wall motion and a mobile apical thrombus (Fig. 1, C and D). Intravenous heparin was begun, but several hours later she had sudden right hemiplegia. A computed tomographic scan was normal. A repeat echocardiogram showed a signif-*

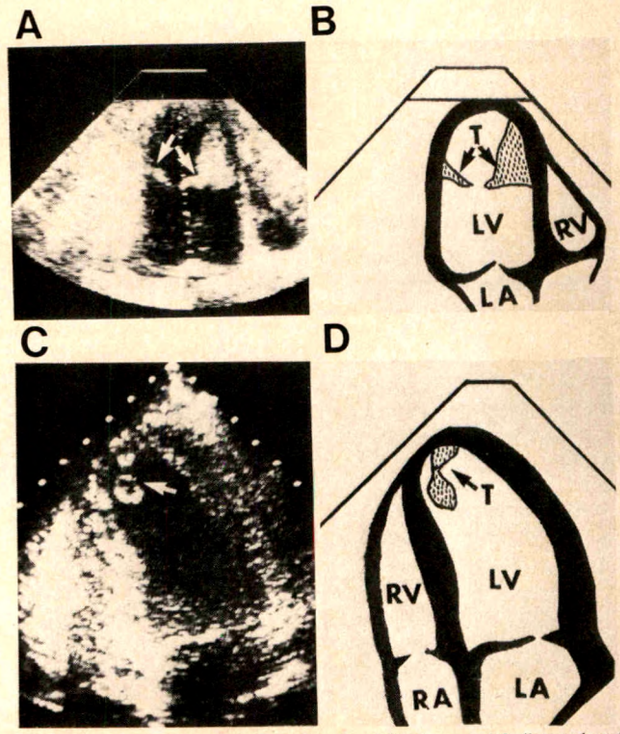

FIGURE 1. A and **B,** representative diastolic frame of 2-dimensional echocardiography in case 1. Note the large thrombus (T) (**arrows**) within the left ventricle (LV). **B** and **C,** a pedunculated apical thrombus in case 2. LA = left atrium; RA = right atrium; RV = right ventricle.

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icant decrease in the size of the thrombus. A diagnosis of cerebral embolism was made and anticoagulant therapy was continued. The patient's condition progressively deteriorated and she died 2 weeks later.

In the 2 patients described, the findings were typical of thrombi; however, in contrast to previous studies,[2,3] the LV wall motion was normal. The occurrence of systemic emboli was confirmed in case 1 and appeared highly likely in case 2. Both patients had a marked decrease in the size of the LV thrombus after the embolic events on follow-up echocardiographic studies. Although the relative role of thrombus mobility could not be adequately defined, it appears reasonable to assume that normal ventricular systolic function was a contributing factor in causing emboli.

The mechanism of development of thrombi in the presence of normal ventricular wall motion is unclear, but it is notable that both patients had an underlying malignant disease that was associated with an increased incidence of thrombosis.[4] In addition, in case 1 there was marked eosinophilia, which in the setting of idiopathic hypereosinophic syndrome has been associated with intracardiac thrombi and embolism.[5]

Prior studies have suggested that 2-dimensional echocardiographic studies are of limited value in the assessment of patients with systemic embolic without clinical evidence of underlying heart disease.[6] Our observations in these 2 patients suggest that 2-dimensional echocardiography may be of value even if underlying heart disease is not suspected. This may be particularly true in patients with an underlying malignancy. The combination of LV thrombi and normal wall motion may increase the likelihood of subsequent embolic events.

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Benign Intracardiac Thyroid Mass Causing Right Ventricular Outflow Tract Obstruction

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The presence of thyroid tissue within the heart is rare. Most reports have described intracardiac metastases from thyroid carcinoma. Herein we describe for the first time a benign intracardiac thyroid mass that was successfully excised.

A 58-year-old woman with past systemic hypertension was noted to have a systolic ejection murmur at age 52 years. By age 58 years the intensity of the murmur had increased to grade 4/6 and was present along the left sternal border. It radiated to the upper sternal area, and an associated palpable thrill was present. The second heart sound was single. The patient had noted recently a slight decrease in exercise tolerance. Chest radiograph revealed a normal-sized heart, clear lungs and a prominent main pulmonary artery. The electrocardiogram revealed borderline right ventricular hypertrophy. On admission to the hospital, a 2-dimensional echocardiogram demonstrated a 2.5 × 1.5 cm, ovoid right ventricular (RV) outflow tract mass attached to the RV side of the ventricular septum, proximal to the pulmonary valve with possible involvement of the cusps. During the cardiac cycle, the mass moved with a ball valve-like motion. The heart was normal in size, configuration and chamber size (Fig. 1). The patient underwent surgical exploration with use of cardiopulmonary bypass. The pulmonary artery was opened, revealing the ovoid mass herniating through the pulmonary valve (Fig. 1). The valve cusps were normal. By retracting the valve cusps, the mass was visualized, originating just below the pulmonary valve and extending down along the ventricular septum with a broad base. The mass

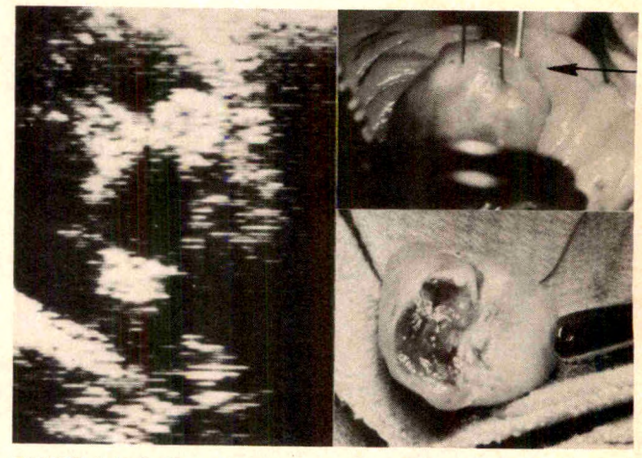

FIGURE 1. Left, frame from 2-dimensional echocardiographic study showing a round mass in the right ventricular outflow track (seen as an echo-dense round mass near center of this frame). **Upper right,** intraoperative photograph of the mass (**arrow**) being delivered into the surgical field through the pulmonary valve. **Lower right,** the excised mass with a muscular margin from the attachment to the ventricular septum.

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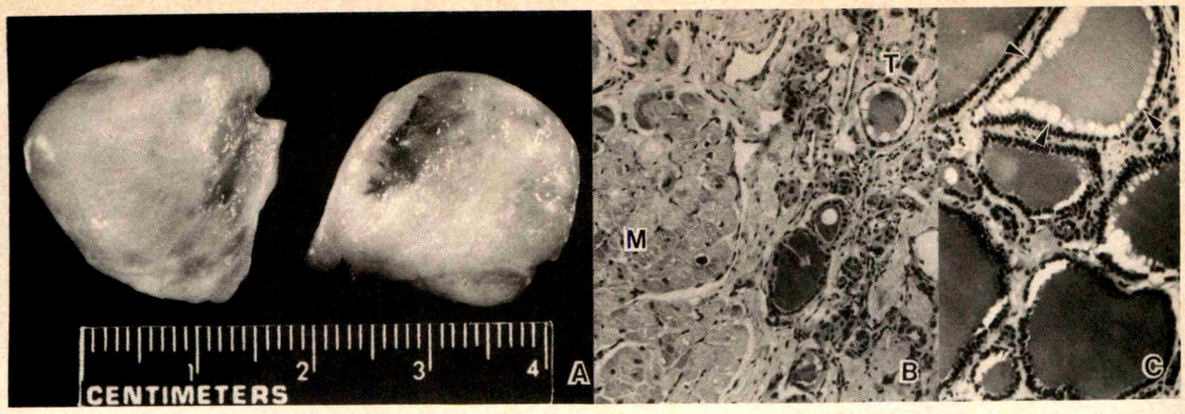

FIGURE 2. A, gross and histologic appearance of surgically resected cardiac thyroid mass. **Left,** external surface; **right,** cut surface. The appearance of the sectioned surface strongly resembles that of the normal thyroid gland. **B,** photomicrograph showing myocardium (M) at **left,** adjacent to large colloid-containing follicles resembling thyroid (T). **C,** photomicrograph showing large follicles and the peripherally scalloped colloid (**arrowheads**) characteristic of hyperplastic thyroid. Hematoxylin-eosin stain; × 325, reduced 35%.

was excised with a margin of normal muscle on the ventricular septum (Fig. 1). The patient recovered uneventfully. The excised mass was "rubbery" and measured 2 × 2 × 1 cm (Fig. 2). The external surface of this mass had a dense fibrous capsule. Microscopically, the mass was composed of thyroid tissue that had variations in follicular size, focal hemorrhage, fibrosis, and calcific and cholesterol deposits consistent with adenomatous hyperplasia. It was not neoplastic and it was consistent with an intracardiac ectopic rest.

Thyroid function tests revealed a T_4 of 8.6 mg% (normal, 5 to 11 mg%), a thyroid binding globulin index of 0.95 (normal, 0.85 to 1.10) and a thyroid stimulating hormone of 2.5 μU/ml (normal, less than 5 μU/ml). A ^{123}I scan revealed a normal thyroid gland in the neck and no evidence of other ectopic foci.

This is the first recorded case of a benign thyroid rest of the RV outflow tract found during life. A previous case was found at autopsy in a 51-year-old woman with a systolic murmur.[1] The patient died of cerebral angioblastoma; at autopsy she was found to have a 4 × 5 × 6 cm mass originating from the RV aspect of the ventricular septum, just below the pulmonary valve and the mass obstructed the RV outflow tract. It too was composed of benign thyroid tissue. She had a normal thyroid gland.

With the exception of our patient and the one reported by Rogers and Kesten,[1] all studies of intracardiac thyroid tissue have reported metastases. A solitary thyroid metastasis to the heart has not been reported. Both cases of benign ectopic thyroid rests originated from the right side of the ventricular septum. During the patients' middle age, they grew to a significant degree to cause RV outflow tract obstruction and a clinical systolic ejection murmur. Both patients had a normal thyroid gland in the neck. The patient described in this report had normal thyroid function. The RV outflow tract is often a site for symptomatic cardiac metastatic tumors and thyroid carcinoma frequently metastasizes to the heart. Although the potential for malignant transformation of intracardiac ectopic thyroid would seem to exist, primary thyroid cancer of the heart has not been reported.[2] Thus, the presence of thyroid tissue in the heart does not portend a poor prognosis; complete resection is indicated and the condition is curable.

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Nonsurgical Treatment of the Superior Vena Cava Syndrome

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Transvenous pacemaker electrodes and any other central venous catheter may cause superior vena cava (SVC) thrombosis. When more than 1 pacemaker electrode is present, contact between the electrodes accentuates the thrombotic tendency and may cause local injury and stenosis of the vessel. We present a patient in whom 2 pacemaker electrodes caused stenosis and thrombosis of the SVC, and the obstruction was subsequently successfully treated with streptokinase and transluminal angioplasty.

A 71-year-old woman had a permanent transvenous pacemaker implanted through the right cephalic vein in 1968 because of complete atrioventricular block. In April 1981, a second wire was inserted, using the left cephalic vein because

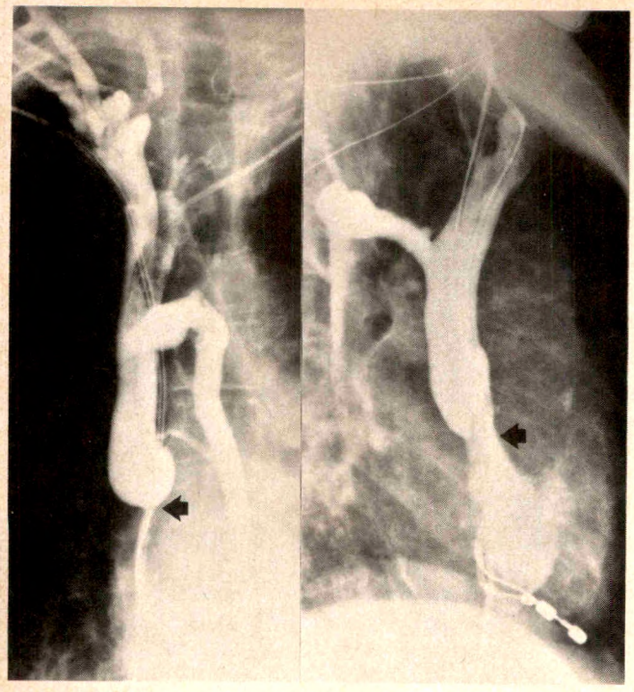

FIGURE 1. Left, upper extremity venogram with subtotal occlusion of the superior vena cava near the right atrium (**arrow**). The azygous vein is distended. **Right,** postangioplasty venogram showing wide patency of the superior vena cava at the previous site of stenosis (**arrow,** lateral projection).

of malfunction of the original lead, which was left in place. The patient did well for 4 months until August 1981, when she awoke with nasal stuffiness and dyspnea, and noted swelling of her eyelids and lips. Cyanosis of the lips, blurred vision and headache were also present. The blood pressure was 145/105 mm Hg, pulse 76 beats/min and respirations 32 breaths/min. Cyanosis and nonpitting edema of the head and thorax were seen. There was pronounced jugular venous distention. Chest roentgenogram on admission showed 2 pacing electrodes, their tips in the right ventricular apex and 1 of the electrodes attached to its battery pack in the left infraclavicular area. The other electrode had been amputated; its free end was below the right clavicle. Bilateral upper-extremity venograms showed extensive thrombosis of the left brachiocephalic and right subclavian veins. The clot extended into the SVC. The patient was treated with streptokinase for 48 hours, heparin therapy for 1 week, and discharged on warfarin sodium after a venogram showed patency of the subclavian and innominate veins and SVC.

The patient did well for 30 months, until April 1984, when she again presented with symptoms of SVC obstruction. A venogram showed occlusion of the SVC. Fibrinolytic therapy was again administered. No relief of the signs or symptoms had occurred at 48 hours and a repeat venogram showed thrombosis and stenosis at the SVC (Fig. 1, left). Percutaneous transluminal angioplasty was performed, initially using a balloon 4 cm long and 12 mm in diameter. After successful dilation, a 20-mm balloon was placed at the stenosis and the area was again dilated. A repeat venogram after the angioplasty showed that the SVC was widely patent (Fig. 1, right). No pulmonary emboli were encountered after the procedure. The patient was discharged in an asymptomatic state after a 12-day hospitalization. She has had no further symptoms in 10 months.

The first report of a complication of pervenous pacing was reported by Prozan et al in 1968.[1] They described a patient who died of multiple pulmonary emboli. On autopsy, the source was identified as clot on the pacing wire. Occasionally, the innominate or subclavian vein will be obstructed after pacemaker insertion. Studies have reported an incidence of partial obstruction of these vessels of between 31 and 50%.[2,3] Up to one-third have total occlusion.[2] Clot may extend into the SVC, but total occlusion here is rare and development of the SVC syndrome is even rarer. Frequently, a malfunctioning pacing wire cannot be removed from the right ventricle because of fibrous entrapment. If a second wire is inserted, stenosis of the vessel may occur at the site of their intersection. Removal of the wire and anticoagulation therapy has been used to prevent further thrombosis and to allow time for development of collateral flow in patients with partial or complete occlusion. This may be effective, even in patients with SVC syndrome. Thrombolytic therapy has been used successfully, although recurrent thrombosis at a later date is frequently seen, and is particularly common in cases where stenosis of the SVC is present in addition to thrombosis.[4] Insertion of a bypass graft is an alternative therapy.

Transluminal angioplasty has been used in the inferior vena cava to dilate stenoses in 5 patients with the Budd-Chiari syndrome.[5] Angioplasty is also helpful in dilating congenital or postoperative venous channels.[6] If the obstruction of the vena cava is purely stenotic or even associated with thrombus, angioplasty may be helpful. If a single balloon is not large enough, 2 or more balloons can be easily used.

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Diagnosis of Cardiac Tumors in Infants by Magnetic Resonance Imaging

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Primary cardiac tumors in infancy are rare, with an estimated necropsy incidence of 0.027%.[1] Traditionally, cardiac catheterization has been used to establish and confirm the diagnosis of intracardiac tumors.[2] Recently, 2-dimensional (2-D) echocardiography has proved to be a reliable, noninvasive tool for diagnosis.[3] We report the use of magnetic resonance imaging (MRI) for evaluation of 4 infants with intracardiac tumors. In each patient, detailed visualization of the intracardiac mass was achieved using an electrocardiogram-gated MRI technique.

MRI was performed with a commercially available superconducting magnetic (Technicare, Inc.) operating at 0.6-tesla field of strength. A multislice technique affording up to 16 adjacent 0.75- to 1-cm sections, depending upon the repetition time (TR), was used and the images were reconstructed with a 2-D Fourier transformation technique. The reconstruction matrix was 128 vertical by 256 horizontal pixels with 256 gray levels. All patients were imaged in coronal, transverse, sagittal and left anterior oblique planes using the multislice technique. Spin-echo pulse sequences were obtained with echo delay times of 30 ms. The TR (in ms) was set according to each patient's heart rate, by the formula (60,000/HR) − 50, with most TR varying between 500 and 1000 ms.

All images were gated using a Hewlett Packard telemeter. The transmitter was placed adjacent to the patient just outside the coil and the receiver was located in the control room. All sequences were initiated on the R wave of the electrocardiogram. All patients were sedated with intramuscular meperidine (2 mg/kg), promethazine (0.5 mg/kg) and chlorpromazine (0.5 mg/kg), given 1 hour before the procedure.

At the time of presentation, all patients had undergone 2-D echocardiography, which established the diagnosis of an intracardiac tumor. Patient age at MRI study ranged from 3 to 12 months. The site of the tumor was the right ventricle in 2 infants, right atrium in 1 infant and left ventricle in 1. Two infants had tuberous sclerosis. One patient (no. 1) had surgery, at which time a rhabdomyoma was removed from the right ventricle. Three patients are currently asymptomatic and 1 patient (no. 4), with a left ventricular tumor, died suddenly at age 13 months.

The electrocardiogram-gated MRI technique afforded excellent visualization of the extent and site of attachment of the tumor in all 4 patients. In patient 1, with a right ventricular tumor, MRI revealed a well circumscribed elliptical mass attached to the right ventricular anterior wall (Fig. 1). In patient 2, the right ventricular tumor was confined to the apex of the ventricle and was attached to the ventricular septum (Fig. 2).

In patient 3, with a right atrial tumor, the mass was well seen on transverse and coronal views. The MRI study showed a large, solitary, spherical mass attached to the lateral wall of the high right atrium near the entry of the superior vena cava (Fig. 3).

In patient 4, with a left ventricular tumor, the MRI study revealed a large left ventricular mass bulging into and significantly compromising the volume of the ventricular

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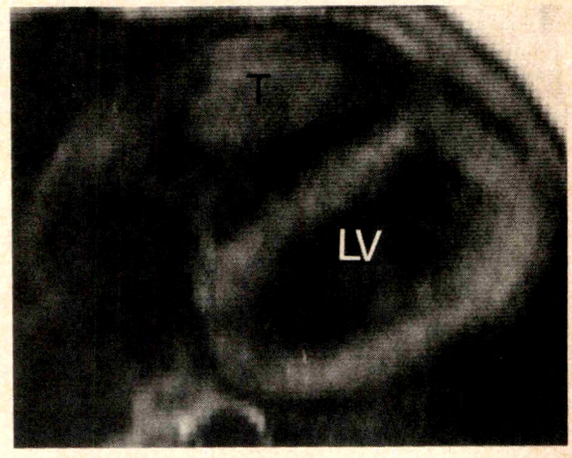

FIGURE 1. Transverse magnetic resonance image at the level of the ventricles. The tumor (T) in the right ventricular cavity is attached to the right ventricular anterior wall. LV = left ventricle.

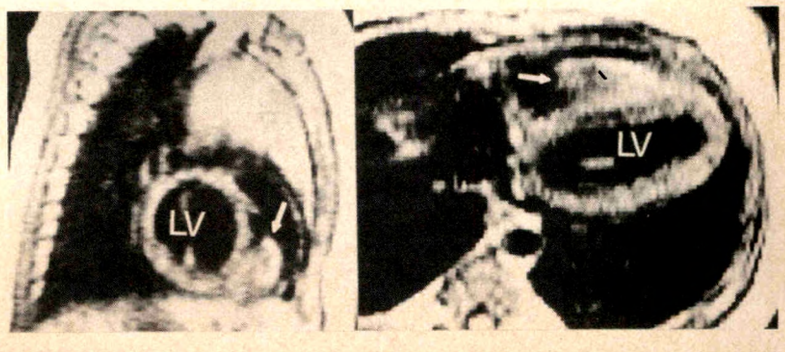

FIGURE 2. Left, patient 2. Sagittal view revealing the right ventricular tumor (**arrow**) attached to the apical region of the ventricular septum. **Right,** transverse section at the level of the ventricles in the same patient. The tumor (**arrow**) adheres to the ventricular septum and is free from the right ventricular anterior wall. LV = left ventricle.

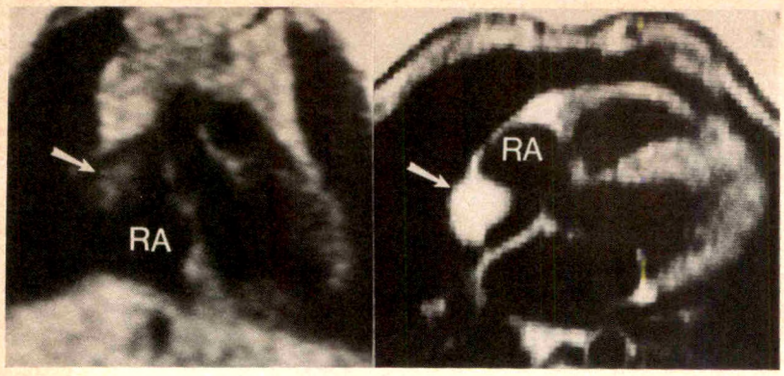

FIGURE 3. Left, patient 3. Coronal view revealing a spherical mass (**arrow**) in the high right atrium. **Right,** transverse 4-chamber image of the same patient. The tumor (**arrow**) adheres to the right atrial wall and protrudes into the right atrial cavity (RA).

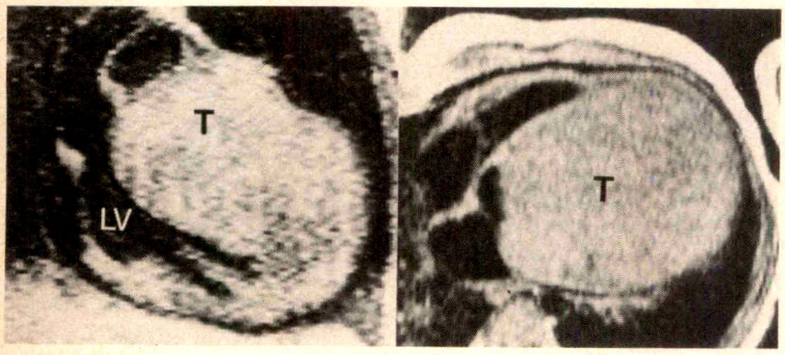

FIGURE 4. Left, patient 4. Coronal image showing a large left ventricular tumor (T) compressing the left ventricular cavity (LV). **Right,** transverse 4-chamber image of the same patient revealing the large left ventricular tumor.

chamber (Fig. 4). The tumor was noted on all imaging planes, but was best visualized on the transverse and coronal views.

Previous studies have shown that electrocardiogram-gated MRI is a safe, noninvasive technique that produces accurate, detailed visualization of intracardiac anatomy in many congenital cardiac defects.[4,5] MRI is ideally suited for cardiovascular studies because of the naturally occurring high degree of contrast between moving blood and the more stationary cardiac tissues. An additional advantage, especially in infants and children, is the lack of need for intravenous contrast agents or exposure to ionizing radiation.

A recent study in adults and children has established the validity of MRI in the evaluation of cardiac and paracardiac masses.[6] In that report, an 18-month-old child with a congenital cardiac tumor was presented. In the current study, with the use of electrocardiographic gating, high-resolution images of intracardiac tumors and their relation to normal cardiac structures were obtained in 4 infants. Because a wider field of view can be obtained and the quality of images is not adversely affected by adjacent lung tissue and bone, the MRI technique afforded excellent delineation of the intracardiac masses.

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Cardiac Hydatid Cyst Simulating Tricuspid Stenosis

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Cardiac echinococcosis is rare, occurring in only 0.5 to 2% of patients with echinococcal disease.[1] Echocardiography has been used to diagnose and detect intracardiac echinococcosis.[2–5] We present a patient with ventricular septal hydatid cyst, diagnosed by 2-dimensional echocardiography, simulating tricuspid stenosis.

A.P., a 23-year-old woman, was admitted complaining of dyspnea on exertion, cough and hemoptysis for 3 months. She was in no distress. The blood pressure was 110/70 mm Hg. The neck veins were distended and the a *wave was prominent. The lungs were clear. A musical diastolic murmur was heard at the left, second and third intercostal area. The electrocardiogram showed sinus tachycardia, right atrial enlargement and incomplete right bundle branch block. Telecardiography showed a prominent right atrial border, mild cardiomegaly and decreased pulmonary vasculature. Tricuspid stenosis was diagnosed by M-mode echocardiography (Fig. 1). Two-dimensional echocardiography disclosed a large cystic tumor with multiple septa on the upper part of the ventricular septum, protruding into the right ventricular cavity and obstructing the tricuspid valve (Fig. 2). Phonocardiography and jugulography showed a prominent* a *wave, early decrescendo and mid-diastolic murmurs (Fig. 1). Right ventricular cineangiography, at which radiopaque material was given in the right atrium, showed 3 lobulated masses protruding into the right ventricle (Fig. 3). The right atrial pressures were elevated. Right ventriculotomy under total cardiopulmonary bypass was performed. A 5 × 3 cm cyst was found under the septal leaflet of the tricuspid valve, localized in the upper third of the ventricular septum. The valve was intact. Numerous germinative membranes and daughter cysts were seen in the cystic cavity. There was no ventricular septal defect at the region where the cyst was based. All of the daughter cysts were removed. After resection of the excess of the pocket, it was closed with Teflon® pledget sutures. The heart began to pump spontaneously. On the second postoperative day, pulmonary edema developed and she died 60 hours after the operation.*

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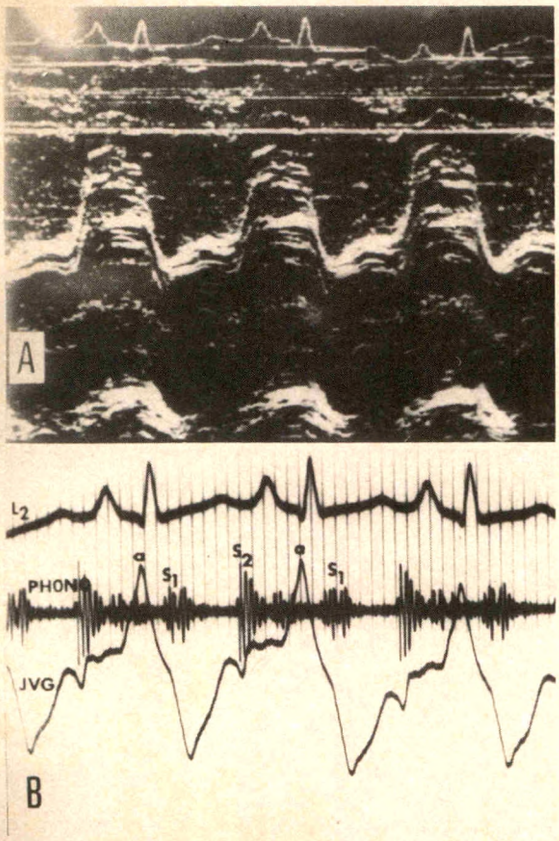

FIGURE 1. A, tricuspid valve showing tricuspid stenosis on M-mode echocardiography. **B,** simultaneous recording of electrocardiogram, phono- and jugulogram. Note the 2 different diastolic murmurs on phono and prominent *a* waves on jugulogram (JVG).

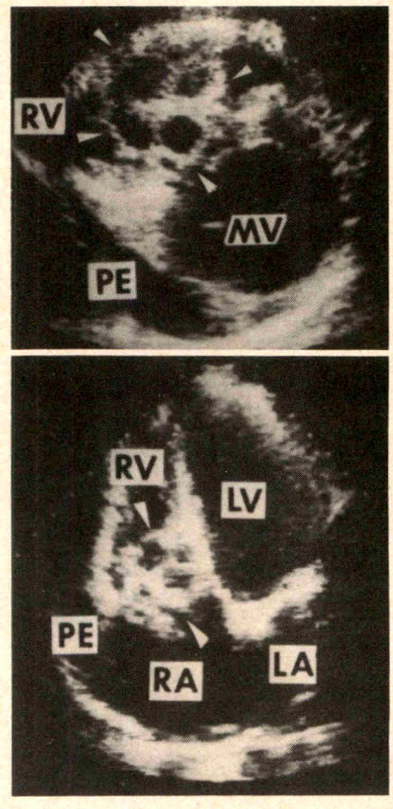

FIGURE 2. Top, 2-dimensional echocardiogram in the short-axis view showing the multiseptated cystic structure (**arrows**) located on the interventricular septum. **Bottom,** apical 4-chamber view showing the same structure (**arrows**) just under the tricuspid valve. LA = left atrium; LV = left ventricle; MV = mitral valve; PE = pericardial effusion; RA = right atrium; RV = right ventricle.

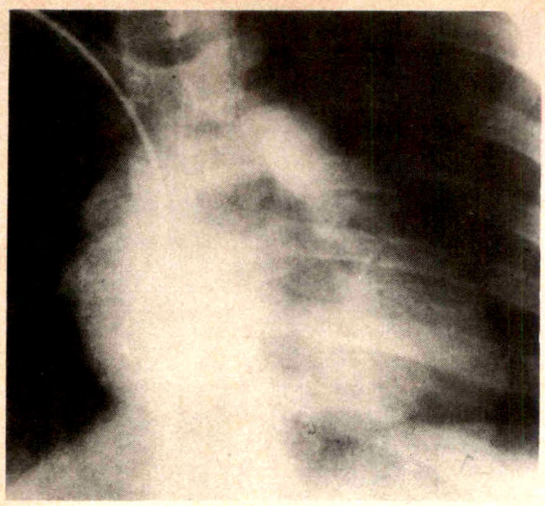

FIGURE 3. Angiographic study of the patient. Posteroanterior view shows 3 lobulated structures in the right ventricle.

Necropsy revealed no ventricular septal defect or cardiac tamponade. The tricuspid valve was intact. The left lung was solid and several cysts were removed from the left main pulmonary artery and its branches. The right lung was seen partially expanded; one of 2 blebs on it had ruptured.

Although there are many reports about hydatid cysts obstructing right ventricular outflow tract, cases with tricuspid valve obstruction are rare.[1,6] In our patient, the cyst was located in the upper third of the ventricular septum of the right side of the heart and simulated tricuspid stenosis. Multiple emboli caused subacute and acute pulmonary hypertension and finally fatal pulmonary insufficiency.

Acknowledgment: We gratefully acknowledge the curiosity of our echo technician, Ayten Solak, who called our attention to the case.

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Echocardiographic Detection of Circulating Blood in Normal Canine Hearts

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Experimental studies by Sigel et al[1] show that blood is echogenic in vitro. The echogenicity of blood also has been demonstrated in vivo but has always been related to reduced blood flow during, for example, left ventricular aneurysm[2] and left atrial dilatation secondary to long-standing mitral valve disease.[3] In the same way, it is possible to observe homogeneous echoes of low acoustic density that are due to blood stasis in the pericardial cavity when it contains liquid blood.[4] This report describes a study in dogs in which the movement of circulating blood was detected by echocardiography.

Nineteen adult mongrel dogs weighing 16 to 32 kg were anesthetized with intravenous sodium pentobarbital, 25 mg/kg, and intubated. Room air ventilation was maintained by means of a Harvard respirator. The chest was opened by a midsternal incision and the pericardium was maintained intact. Fluid-filled 5Fr polyvinyl catheters were inserted through the superior vena cava and carotid artery. Right atrial, right ventricular, pulmonary artery, aortic and left ventricular pressures were recorded using a Gould transducer and a Siemens Minograph 82. Cardiac output was measured by thermodilution; a Swan-Ganz catheter was placed in the pulmonary artery through a jugular vein and an Edwards 9500 A cardiac output computer was used. Three successive determinations were made, and the average was calculated.

Several short- and long-axis views were obtained by placing the transducer directly on the heart, taking special care not to press on the cavity. A Mark 600 ATL echocardiograph with a 7-MHz transducer was used. In 4 dogs, images were also obtained with a 3-MHz transducer. In all dogs a simultaneous M-mode recording was made in the zone where the echoes produced by the blood were more intense. Special care was taken to set the echocardiograph controls in a high-gain setting to facilitate recording of the echoes produced by the blood. With a low-gain setting these images were less visible. All studies were recorded on a Panasonic VHS vidoetape recorder for subsequent analysis. Echocardiographic images were recorded before and after the introduction of catheters into the heart cavities and no differences were observed between them.

In the right ventricular cavities of 16 dogs, intracavitary echoes showing dynamic variations in shape and conformation from beat to beat were obtained. Intracavitary echoes were characterized by low amplitude and variable density, showing a circular, whirlpool-like movement. The maximal echo intensity was observed between the leaflets of the tricuspid valve in diastole. The correspondent M-mode image was recorded as a set of linear echoes, similar to those found

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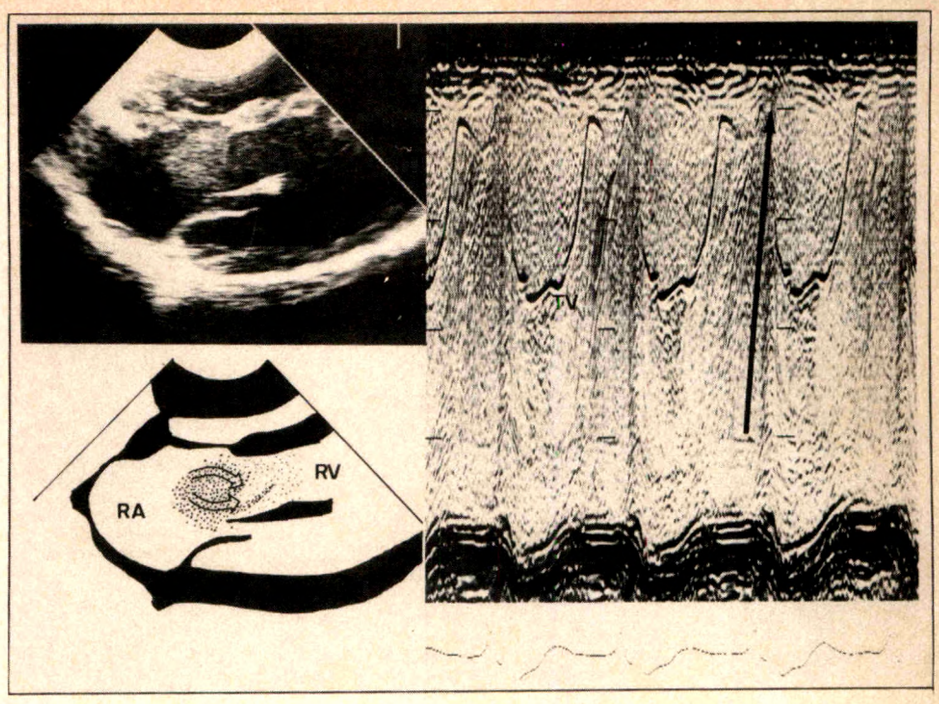

FIGURE 1. Top left, 2-dimensional echocardiogram, parasternal long-axis view of the right ventricle (RV). **Bottom left,** dynamic echoes (**curved arrows**) produced by blood can be seen between the anterior and posterior tricuspid leaflets. **Right,** M-mode echocardiogram at the level of the tricuspid valve (TV), showing the echoes produced by blood passing through the tricuspid valve in diastole. Note the increase of the echoes when atrial contraction occurs (**long arrow**). RA = right atrium; RV = right ventricle.

in right cavities by contrast echocardiography, particularly at the time of tricuspid valve opening. In all dogs an evident increase in the intensity of the echoes during atrial systole, coincident with the tricuspid "a" wave in the M-mode echocardiography, was produced (Fig. 1).

Images of the left ventricular cavity, similar to those of the right side, were observed in 6 dogs, 3 of them also showing echoes in the right-sided cavities. Whirlpool-like echoes, showing clear phasic variations in shape from beat to beat, which were indicative of a fluid state, were recorded by 2-dimensional echocardiography (Fig. 2); the maximal intensity was in the left ventricular cavity. Using M-mode echocardiography, stratified linear echoes were observed in the same 6 dogs. In the other 3 dogs, no intracavitary echoes were observed throughout the study.

In all dogs, cardiac output was within the normal range (mean 110 ± 16 ml/kg). There was no significant difference compared with a group of normal dogs previously studied in our laboratory (cardiac output 100 ± 30 ml/kg) (unpublished observation). Right- and left-sided pressures were always within the normal range.

For the first time, our results show that blood can be echogenic in the absence of blood stasis under experimental conditions. The causes of this finding are related to the special characteristics of the study, because the technical aspects of the echocardiographic examination and the ultrasonic frequency are important factors in any study on the acoustic properties of blood. We used a 7 MHz transducer placed directly on the heart. Longitudinal and lateral or angular resolution increases when using high-frequency echo transducers, despite the decrease in depth of penetration.[5] This increase in resolution probably permits images of blood in the fluid state to be obtained. In 4 dogs we used a 3-MHz transducer and could not visualize the blood echoes that were

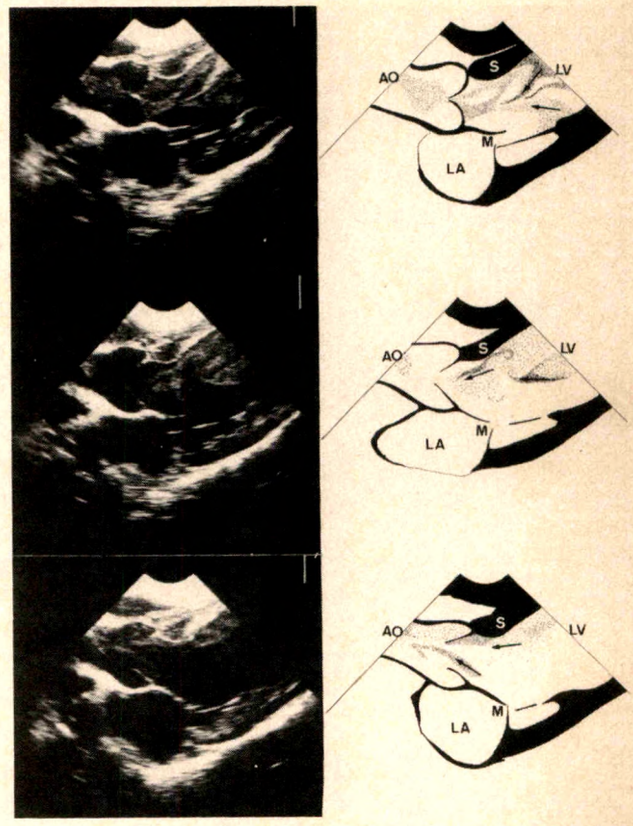

FIGURE 2. Two-dimensional echocardiogram, parasternal long-axis view of the left ventricle (LV) showing whirlpool-like echoes that show evident phasic variations in formation from 1 cardiac cycle to another, indicative of a fluid state. AO = ascending aorta; LA = left atrium; M = mitral valve; S = ventricular septum.

easily seen with the 7-MHz transducer. This finding is in accordance with the studies of Mikell et al,[2] who showed that the echocardiographic patterns of blood stasis in dogs with important segmental contraction abnormalities were more easily seen with a 5-MHz than with a 3-MHz transducer. Likewise, in patients with apical wall motion abnormalities, the echocardiographic pattern of blood stasis observed when using a 5-MHz transducer is only scarcely visible when using a 3-MHz transducer.[2]

As our data indicate, the echocardiographic images of circulating blood are detected more frequently in the right ventricular cavity. Several factors can be adduced to explain these findings. The left ventricle is situated more deeply than the right ventricle and, because of the reduction in depth penetration of high-frequency transducers, it would be more difficult to obtain well-defined images from very deep areas of the heart. Nevertheless, there must be some factors other than the depth that can facilitate the appearance of blood echogenicity in the right ventricle. In 4 dogs the short-axis view showed echocardiographic images of blood flow in the right atrium and the right ventricle but not in the aorta, even though the aorta is closer to the transducer than the right atrium in this view. The better visualization of venous blood compared with arterial blood can probably be explained by their different physicochemical and rheologic characteristics. Density and viscosity of blood increase with a higher content of CO_2.[6] Therefore, viscosity and density are greater in venous blood than in arterial blood, a factor that may facilitate echogenicity.

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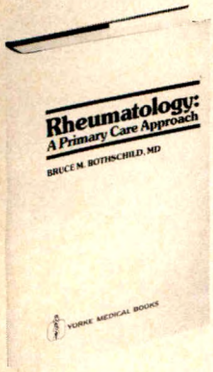

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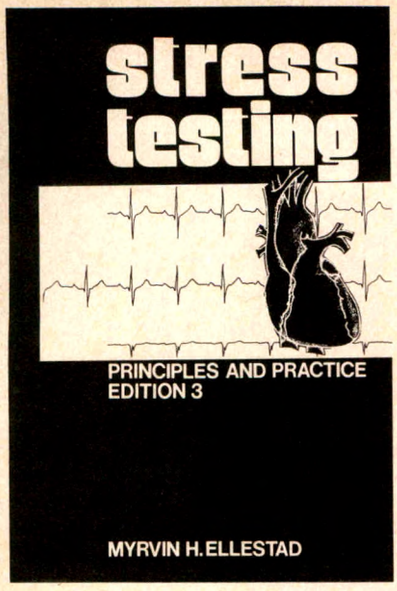

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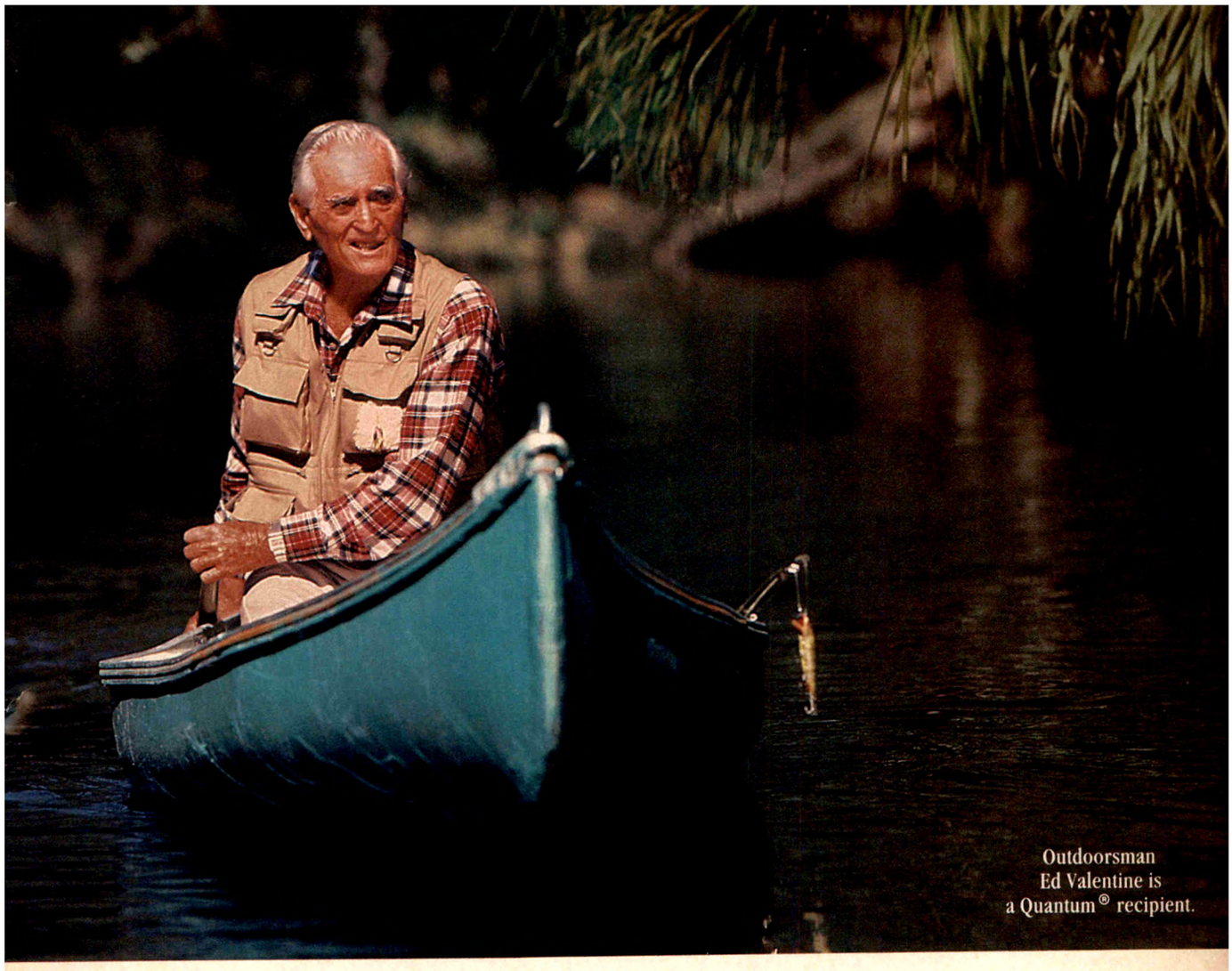

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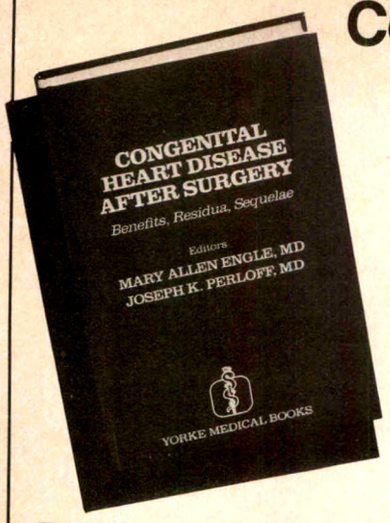

Congenital Heart Disease After Surgery

Benefits, Residua, Sequelae

edited by **Mary Allen Engle, MD**
Joseph K. Perloff, MD

ISBN 0-914316-37-0, 438 pp., November 1983, $40.00

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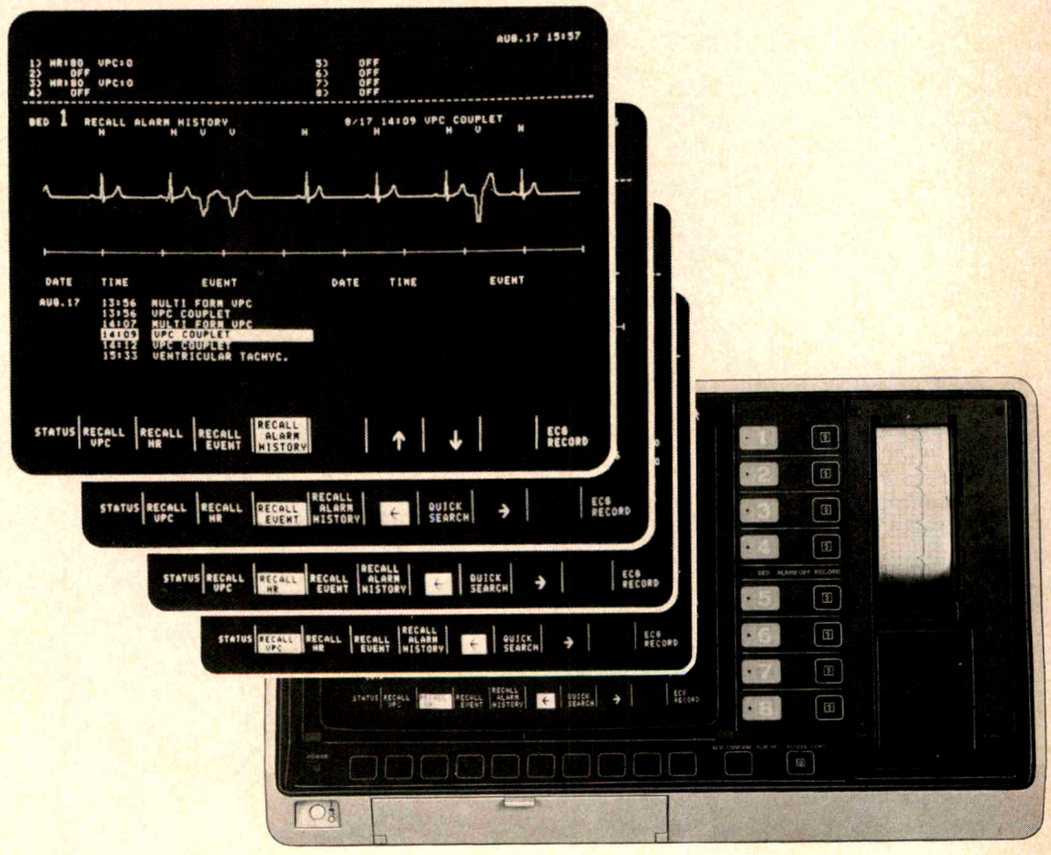

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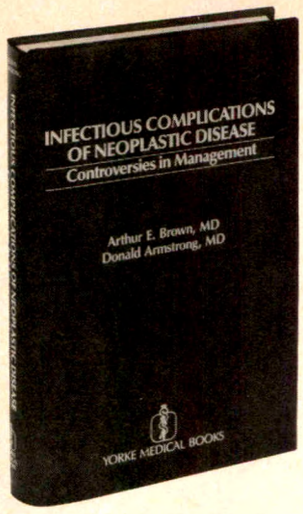

INFECTIOUS COMPLICATIONS OF NEOPLASTIC DISEASE

Controversies in Management

Edited by Arthur E. Brown, MD, and Donald Armstrong, MD
0-914316-43-5, approx. 400 pp., Oct. 1984, $40.00 casebound

About the book

Derived from a symposium sponsored by the Infectious Disease Service, Department of Medicine and the Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York City, and Cornell University Medical College, New York City, this book presents the latest thinking by international authorities, all of whom were invited to present findings in their area of expertise on the diagnosis, treatment, and prevention of various bacterial, fungal, viral, and parasitic infections presenting in patients with neoplastic disease.

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About the Editors

Arthur E. Brown, MD, is Assistant Attending Physician, Memorial Sloan-Kettering Cancer Center, and Assistant Professor of Medicine and Pediatrics, Cornell University Medical College.

Donald Armstrong, MD, is Attending Physician; Chief of Service; Director, Microbiology Laboratory, Memorial Sloan-Kettering Cancer Center, and Professor of Medicine, Cornell University Medical College

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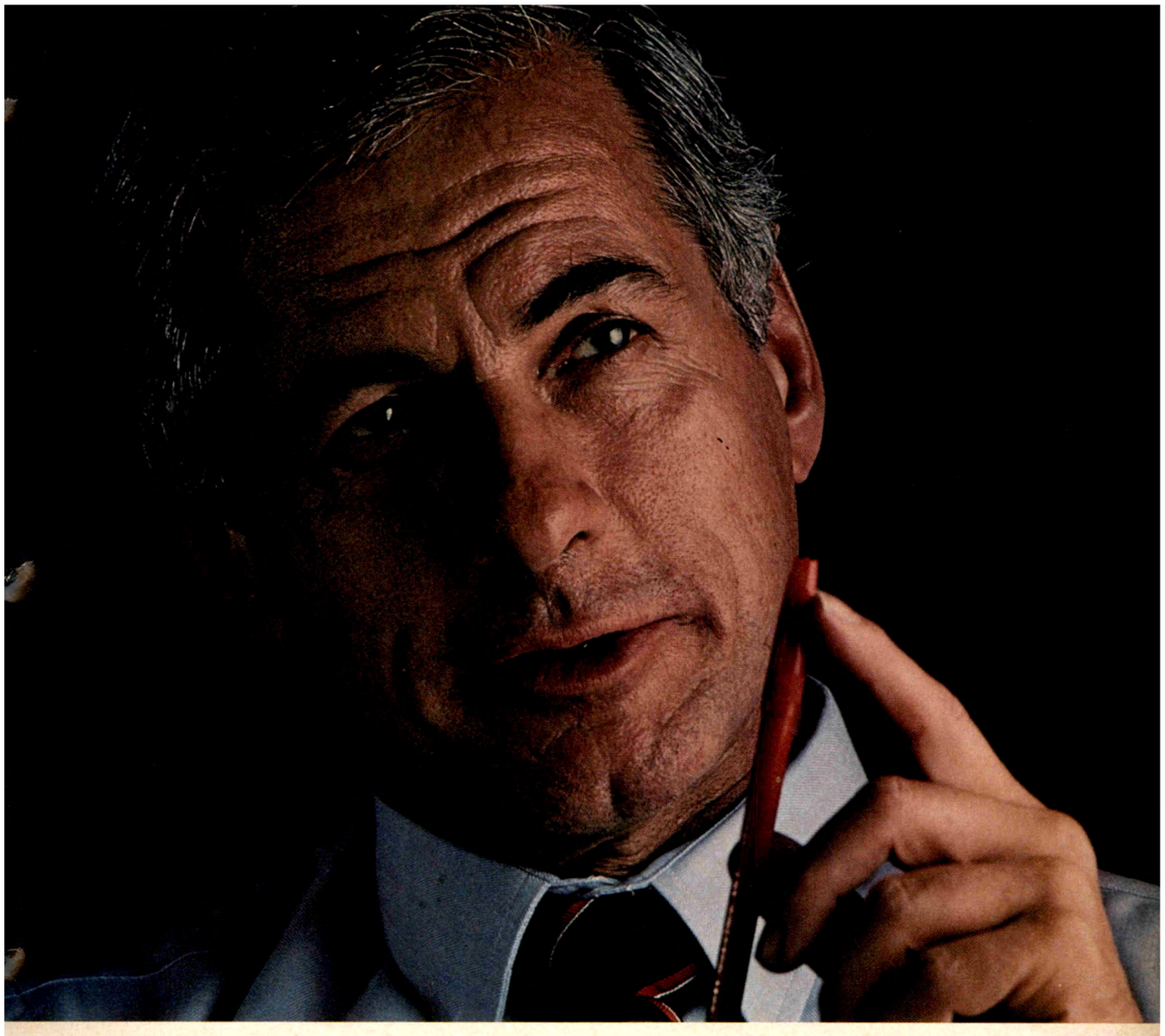

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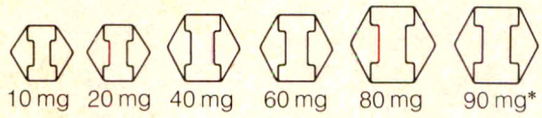

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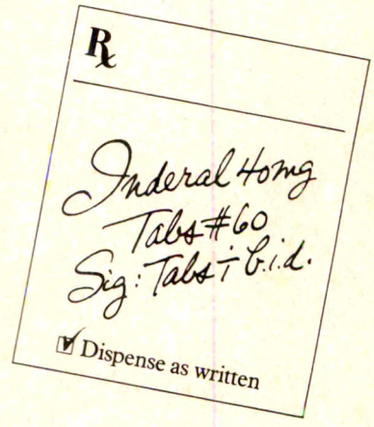

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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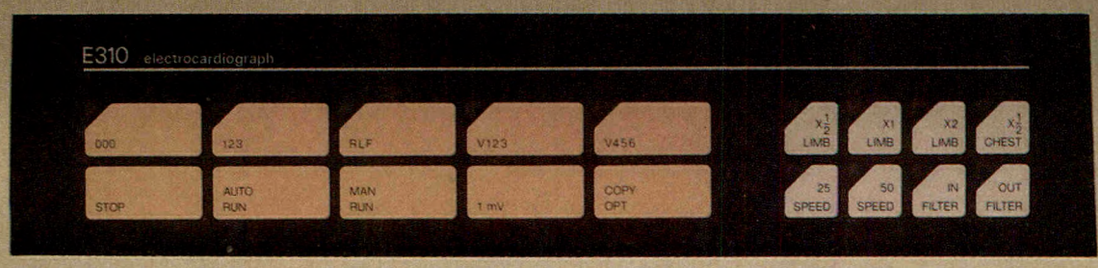
WHY PAY FOR MORE THAN YOU USE? BURDICK'S E 310



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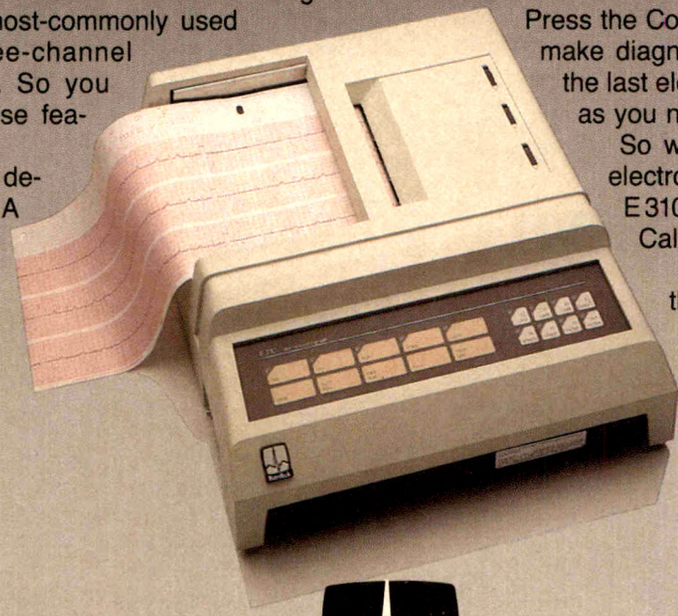

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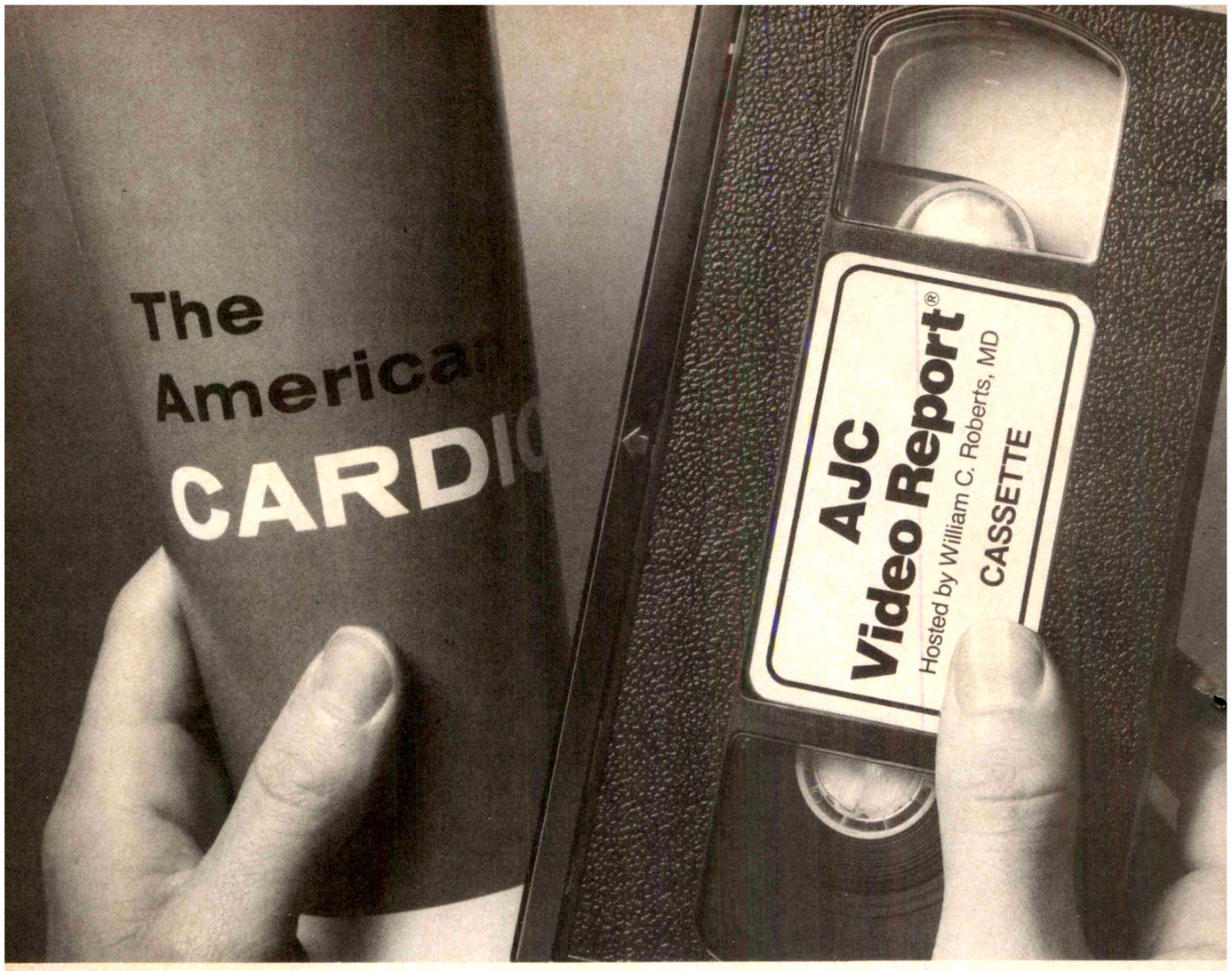

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The American Journal of Cardiology

The AJC in November 1960

WILLIAM C. ROBERTS, MD

The AJC in November 1960 contained 24 articles occupying 147 pages. This piece describes 5 articles.

Before antihypertension therapy, about 90% of patients with *systemic hypertension associated with papilledema* died within 1 year of diagnosis. Early articles on therapeutic effects of ganglionic blocking drugs described follow-up of patients for up to 3 years. Sokolow and Perloff[1] from San Francisco, California, described 5-year results of treatment of 26 patients with malignant hypertension (papilledema plus diastolic arterial pressure >120 mm Hg) with ganglionic blocking agents. Symptoms improved in all 26 patients and the diastolic pressures were reduced >20 mm Hg in 24 patients (92%). Papilledema disappeared in 19 patients (73%). Of 15 patients with poor renal function, improvement in renal function occurred in 7 (47%). The average survival of the 26 patients was 21 months; the 11 with good renal function before therapy survived an average of 39 months and the 15 with poor renal function an average of 8 months.

Shubin et al[2] from Los Angeles, California, described cardiovascular findings in 7 children with *sickle cell anemia* (blood hematocrits 18 to 27%). All 7 had normal pulmonary arterial pressures, normal or high cardiac indexes, and decreased systemic arterial oxygen saturations (77 to 89%). The heart rates at rest were 90 to 100 beats/min. All 7 had precordial systolic murmurs (grade 2/6 or greater), 5 had third heart sounds, all 7 had enlarged cardiac silhouettes on chest radiographs and 4 had abnormalities on electrocardiogram.

Hoffman and Lowrey[3] from Los Angeles, California, described electrocardiographic observations in 123 patients with *hyperthyroidism:* atrial fibrillation in 15 (12%); PR interval >0.20 second in 11 (9%); shortened QT interval in 18 patients (15%); ST-T abnormalities in 28 patients (23%); and heart rates at rest >100 beats/min in 46 patients (37%). The ST-T changes often were transient.

Baker et al[4] from Baltimore, Maryland, administered thyroid stimulating hormone (TSH), 25 mg/day intramuscularly, to each of 5 clinically euthyroid men for 4 or 5 successive days; 4 had electrocardiographic abnormalities during and immediately after the period of TSH stimulation. The abnormalities were those of increased irritability and altered repolarization.

Glover et al[5] from Philadelphia, Pennsylvania, described results of bilateral *ligation and division of the internal mammary artery* in 239 patients, of whom 219 were followed 12 to 30 months postoperatively. Of the 219 patients, 212 had angina pectoris (at rest in 115 patients) preoperatively, and 7 had no angina (recurring pulmonary edema in 4 and "serious arrhythmias" in 3). Of the 219 patients, 119 (54%) had electrocardiographic evidence of recent or healed myocardial infarction. At follow-up, 12 to 30 months postoperatively, 55 patients (25%) were markedly improved, 46 patients (21%) moderately improved, and 38 patients (17%) slightly improved. In 38 patients (17%) there was no improvement and 42 patients (20%) were dead. Only 24 patients (14%) changed in their clinical status 12 to 30 months postoperatively compared with their 1-month postoperative evaluation. Of course, objective evidence of decreased myocardial ischemia in their patients is lacking and coronary angiography was not available for their patients.

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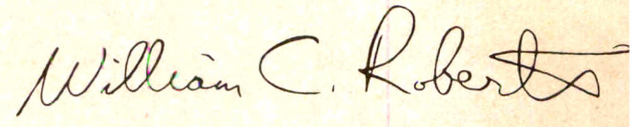
1. **Sokolow M, Perloff D.** Five-year survival of consecutive patients with malignant hypertension treated with antihypertensive agents. Am J Cardiol 1960;6:858–863.
2. **Shubin H, Kaufman R, Shapiro M, Levinson DC.** Cardiovascular findings in children with sickle cell anemia. Am J Cardiol 1960;6:875–885.
3. **Hoffman I, Lowrey RD.** The electrocardiogram in thyrotoxicosis. Am J Cardiol 1960;6:893–904.
4. **Baker SP, Landowne M, Gaffney GW.** Electrocardiographic changes following the administration of thyroid stimulating hormone (thyrotropin). Am J Cardiol 1960;6:905–914.
5. **Glover RP, Kitchell JR, Devila JC, Barkley HT Jr.** Bilateral ligation of the internal mammary artery in the treatment of angina pectoris. Experimental and clinical results. Am J Cardiol 1960;6:937–945.

How Long Do Physicians Live?

In the USA today (1980 life tables), life expectancy from birth for white females is 78.1 years, for black females, 72.3 years, for white males, 70.7 years, and for black males, 63.7 years.[1] For persons who have reached age 25 years in the USA, an age reached by >95% of persons at the time of graduation from medical school, life expectancy is even greater. Thus, of persons reaching age 25 years, 54.5 additional years (to age 79.5) can be expected for white women and 49.5 additional years (to age 74.5) for black women, 47.8 additional years for white men (to age 72.8) and 41.7 additional years for black men (to age 66.7).[1]

Although physicians, of course, are included in these 1980 statistics, these expected ages are not reached by most USA graduates of USA medical schools. In the *Journal of the American Medical Association* each week is a column entitled "Obituaries." Included in it are the names of recently deceased physicians, their ages at death, the name of the medical school from which they graduated, frequently the American specialty board by which they were certified, and the date of their death. Their race is not included. For the 3 years 1981, 1982 and 1983 the age at death of the male and female physicians according to speciality was determined and the results of these tabulations are summarized in the accompanying table.

The table discloses 3 clear findings: (1) the average age at death of both the male and female physicians was below the national average for persons who had reached age 25 years; (2) the mean age of death of the female physicians was younger than that of their male counterparts; and (3) the mean age at death varied among the various subspecialties. The 9,705 male physicians lived a total of 689,184 years, an average of 71.0 years each; the 365 female physicians lived a total of 25,495 years, an average of 69.9 years each. Among the various subspecialties, those surviving the shortest periods on the average were neurosurgeons (58.9 years), anesthesiologists (58.9 years), family practitioners (62.4 years) and pathologists (63.9 years). The longest survivors on the average were those classified as both ophthalmologists and otolaryngologists (79.3 years), next those classified as otolaryngologists (76.7 years), and then those boarded in preventive medicine (74.4 years). The pediatricians survived on an average longer than did the internists (69.2 years vs 66.7 years). The specific numbers on survival for adult cardiologists, pediatric cardiologists, and cardiovascular surgeons are not available.



William C. Roberts, MD
Editor in Chief

1. National Center for Health Statistics. Vital Statistics of the United States, 1980, Vol. II, Sec. 6, Life Tables, DHHS Pub. No. (PHS) 84-1104. Public Health Service, Washington, D.C., U.S. Govt. Print. Off., 1984, 16 pp.

Mean Length of Survival of Physicians Listed in the Obituaries Section of the Journal of the American Medical Association, 1981, 1982 and 1983

	Men		Women		Totals		
Speciality	No.	Mean Age at Death (year)	No.	Mean Age at Death (year)	No.	Total Years	Mean Age at Death (year)
Unspecified	6,182	72.7	254	70.9	6,436	467,667	72.7
Internal medicine	514	66.8	13	61.0	527	35,149	66.7
Surgery	409	67.0	4	72.0	413	27,706	67.1
Obstetrics & gynecology	355	68.6	8	73.9	363	24,943	68.7
Psychiatry & neurology	303	68.7	20	72.7	323	22,259	68.9
Pediatrics	267	69.5	12	63.0	279	19,305	69.2
Radiology	216	67.1	6	82.8	222	14,988	67.5
Pathology	200	64.1	7	58.7	207	13,230	63.9
Opthalmology (Op)	182	70.1	3	80.7	185	13,007	70.3
Otolaryngology (Ot)	176	76.6	2	82.0	178	13,643	76.7
Orthopedic surgery	159	67.0	0	. . .	159	10,656	67.0
Urology	152	71.5	0	. . .	152	10,871	71.5
Family practice	151	62.7	6	54.8	157	9,800	62.4
Anesthesiology	107	59.2	10	55.8	117	6,891	58.9
Dermatology	82	71.2	6	81.0	88	6,323	71.9
Preventive medicine	72	74.5	6	73.0	78	5,801	74.4
Thoracic surgery	40	66.0	2	65.5	42	2,769	65.9
Neurosurgery	17	58.9	0	. . .	17	1,001	58.9
Op + Ot	15	79.3	0	. . .	15	1,190	79.3
Plastic surgery	7	64.0	0	. . .	7	448	64.0
All Others	99	67.6	6	56.8	105	7,032	67.0
Totals	9,705	71.0	365	69.9	10,070	714,679	71.0

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Reduce fluid volume and improve hemodynamics in CHF

Edema due to congestive heart failure often demands highly effective diuresis to reduce the fluid load on the failing heart. Bumex® (bumetanide/Roche) is the next generation in loop diuretic therapy for three powerful reasons. It moves out an unsurpassed volume of fluid and sodium, resulting in significant reductions in edema and right atrial and pulmonary artery wedge pressures.[1,2] It's almost completely absorbed through the GI tract, so it's easy to titrate.[3] And Bumex completes high-volume diuresis fast—within four hours at usual doses.[4,5] Your patients spend less time in diuresis, more time in normal activities.

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0.5-mg and 1-mg scored tablets/2-ml ampuls, 2-ml, 4-ml and 10-ml vials (0.25 mg/ml)

The next generation in loop diuretic therapy

Please see following page for references and a summary of product information.
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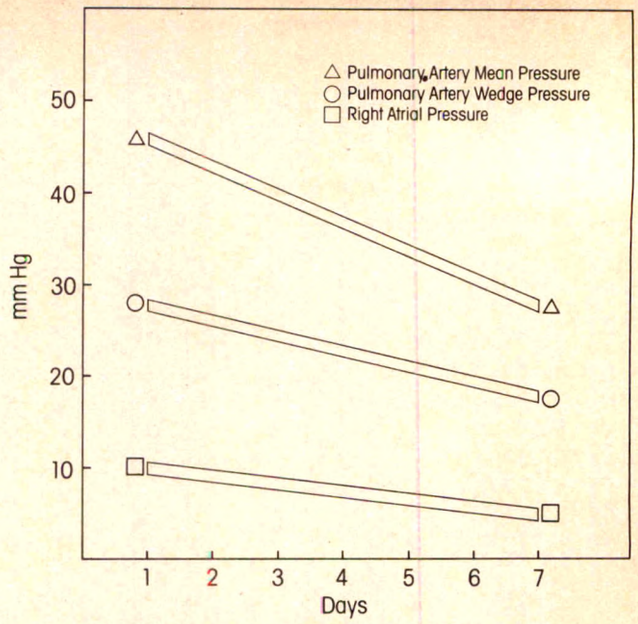
REDUCES FLUID OVERLOAD and eases the burden on the failing heart

Significantly improves hemodynamics



Ten patients with CHF showed marked hemodynamic improvement after seven days of BUMEX® (bumetanide/Roche) (mean values ± SE). Adapted from Olesen, *et al.*[1]

References: **1.** Olesen KH, *et al: Postgrad Med J 51*(Suppl 6):54-63, 1975. **2.** Handler B, Dhingra RC, Rosen KM: *J Clin Pharmacol 21*:706-711, Nov-Dec 1981. **3.** Brater DC, *et al: Clin Pharmacol Ther 34*:207-213, Aug 1983. **4.** Brater DC, Fox WR, Chennavasin P: *J Clin Pharmacol 21*:599-603, Nov-Dec 1981. **5.** Davies DL, *et al: Clin Pharmacol Ther 15*:141-155, Feb 1974.

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WARNING: Bumex (bumetanide/Roche) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dosage schedule have to be adjusted to the individual patient's needs. (See under DOSAGE AND ADMINISTRATION in complete product information.)

INDICATIONS AND USAGE: Edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.
Almost equal diuretic response occurs after oral and parenteral administration of Bumex.
If impaired gastrointestinal absorption is suspected or oral administration is not practical, Bumex should be given by the intramuscular or intravenous route.
Successful treatment with Bumex following instances of allergic reactions to furosemide suggests a lack of cross-sensitivity.
CONTRAINDICATIONS: Anuria. Hypersensitivity and in patients in hepatic coma or in states of severe electrolyte depletion. Although Bumex can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or creatinine, or the development of oliguria during therapy of patients with progressive renal disease, is an indication for discontinuation of treatment.
WARNINGS: Dose should be adjusted to patient's needs. Excessive doses or too frequent administration can lead to profound water loss, electrolyte depletion, dehydration, reduction in blood volume and circulatory collapse with the possibility of vascular thrombosis and embolism, particularly in elderly patients.
Prevention of hypokalemia requires particular attention in patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis and ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diarrheal states, or other states where hypokalemia is thought to represent particular added risks to the patients.
In patients with hepatic cirrhosis and ascites, sudden alterations of electrolyte balance may precipitate hepatic encephalopathy and coma. Treatment in such patients is best initiated in the hospital with small doses and careful monitoring of the patient's clinical status and electrolyte balance. Supplemental potassium and/or spironolactone may prevent hypokalemia and metabolic alkalosis in these patients.
In cats, dogs and guinea pigs, Bumex has been shown to produce ototoxicity. Since Bumex is about 40 to 60 times as potent as furosemide, it is anticipated that blood levels necessary to produce ototoxicity will rarely be achieved. The potential for ototoxicity increases with intravenous therapy, especially at high doses.
Patients allergic to sulfonamides may show hypersensitivity to Bumex.
PRECAUTIONS: Measure serum potassium periodically and add potassium supplements or potassium-sparing diuretics, if necessary. Periodic determinations of other electrolytes are advised in patients treated with high doses or for prolonged periods, particularly in those on low salt diets.
Hyperuricemia may occur. Reversible elevations of the BUN and creatinine may occur, especially with dehydration and in patients with renal insufficiency. Bumex may increase urinary calcium excretion.
Possibility of effect on glucose metabolism exists. Periodic determinations of blood sugar should be done, particularly in patients with diabetes or suspected latent diabetes.
Patients should be observed regularly for possible occurrence of blood dyscrasias, liver damage or idiosyncratic reactions.
Especially in presence of impaired renal function, use of parenterally administered Bumex should be avoided in patients to whom aminoglycoside antibiotics are also being given, except in life-threatening conditions.
Drugs with nephrotoxic potential and bumetanide should not be administered simultaneously.
Since lithium reduces renal clearance and adds a high risk of lithium toxicity, it should not be given with diuretics.
Probenecid should not be administered concurrently with Bumex.
Concurrent therapy with indomethacin not recommended.
Bumex may potentiate the effects of antihypertensive drugs, necessitating reduction in dosage.
Interaction studies in humans have shown no effect on digoxin blood levels.
Interaction studies in humans have shown Bumex to have no effect on warfarin metabolism or on plasma prothrombin activity.
Pregnancy: Bumex should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.
Bumetanide may be excreted in breast milk.
Pediatric Use: Safety and effectiveness below age 18 not established.
ADVERSE REACTIONS: Muscle cramps, dizziness, hypotension, headache and nausea, and encephalopathy (in patients with preexisting liver disease).
Less frequent clinical adverse reactions are weakness, impaired hearing, rash, pruritus, hives, electrocardiogram changes, abdominal pain, arthritic pain, musculoskeletal pain and vomiting.
Other clinical adverse reactions are vertigo, chest pain, ear discomfort, fatigue, dehydration, sweating, hyperventilation, dry mouth, upset stomach, renal failure, asterixis, itching, nipple tenderness, diarrhea, premature ejaculation and difficulty maintaining an erection.
Laboratory abnormalities reported are hyperuricemia, azotemia, hyperglycemia, increased serum creatinine, hypochloremia, hypokalemia, hyponatremia, and variations in CO_2 content, bicarbonate, phosphorus and calcium. Although manifestations of the pharmacologic action of Bumex, these conditions may become more pronounced by intensive therapy.
Diuresis induced by Bumex may also rarely be accompanied by changes in LDH, total serum bilirubin, serum proteins, SGOT, SGPT, alkaline phosphatase, cholesterol, creatinine clearance, deviations in hemoglobin, prothrombin time, hematocrit, platelet counts and differential counts. Increases in urinary glucose and urinary protein have also been seen.
DOSAGE AND ADMINISTRATION:
Oral Administration: The usual total daily dosage is 0.5 to 2.0 mg and in most patients is given as a single dose.
Parenteral Administration: Administer to patients (IV or IM) with GI absorption problem or who cannot take oral. The usual initial dose is 0.5 to 1 mg given over 1 to 2 minutes. If insufficient response, a second or third dose may be given at 2 to 3 hour intervals up to a maximum of 10 mg a day.
HOW SUPPLIED: *Tablets,* 0.5 mg (light green) and 1 mg (yellow), bottles of 100 and 500; Prescription Paks of 30; Tel-E-Dose® cartons of 100. Imprint on tablets: 0.5 mg—ROCHE BUMEX 0.5; 1 mg—ROCHE BUMEX 1.
Ampuls, 2 ml, 0.25 mg/ml, boxes of ten.
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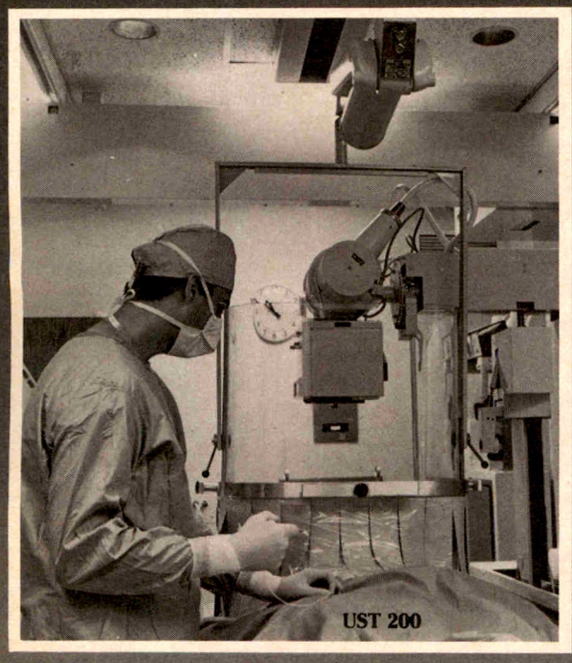

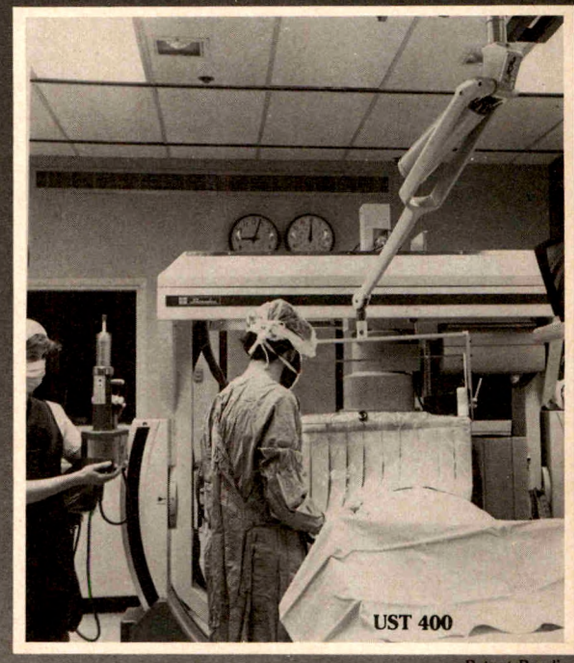

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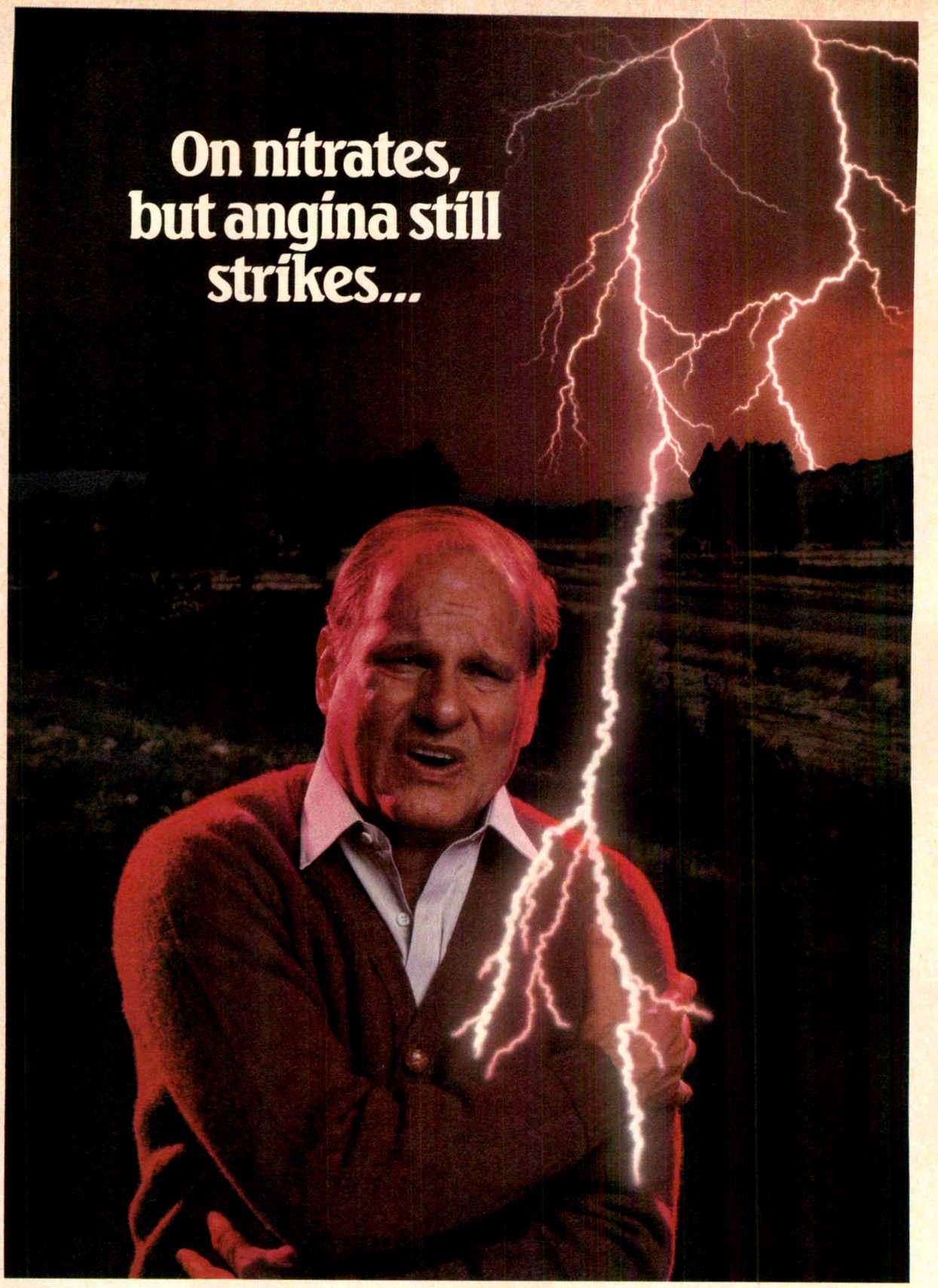
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but angina still
strikes...

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To protect your patients, as well as their quality of life, add Isoptin instead of a beta blocker.

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With Isoptin, fatigue, bradycardia and mental depression are rare. Unlike beta blockers, Isoptin can safely be given to patients with asthma, COPD, diabetes or peripheral vascular disease. Serious adverse reactions with Isoptin are rare at recommended doses; the single most common side effect is constipation (6.3%).

Cardiovascular contraindications to the use of Isoptin are similar to those of beta blockers: severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no artificial pacemaker is present) and second- or third-degree AV block.

So, the next time a nitrate is not enough, add Isoptin... for more comprehensive antianginal protection without side effects which may cramp an active life style.

ISOPTIN. Added antianginal protection without beta-blocker side effects.

Please see brief summary on following page.

ISOPTIN®
(verapamil HCl/Knoll)
80 mg and 120 mg scored, film-coated tablets

Contraindications: Severe left ventricular dysfunction (see *Warnings),* hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction < 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. (See *Precautions.)* Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before ISOPTIN is used. (Note interactions with digoxin under *Precautions.*) ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild and controlled by decrease in ISOPTIN dose). Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment; however, four cases of hepatocellular injury by verapamil have been proven by rechallenge. Periodic monitoring of liver function is prudent during verapamil therapy. Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN. Because of verapamil's effect on AV conduction and the SA node, 1° AV block and transient bradycardia may occur. High grade block, however, has been infrequently observed. Marked 1° or progressive 2° or 3° AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2° AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%), elevations of liver enzymes have been reported. (See *Warnings.*) The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: ecchymosis, bruising, gynecomastia, psychotic symptoms, confusion, paresthesia, insomnia, somnolence, equilibrium disorder, blurred vision, syncope, muscle cramp, shakiness, claudication, hair loss, macules, spotty menstruation. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in round, scored, film-coated tablets containing either 80 mg or 120 mg of verapamil hydrochloride and embossed with "ISOPTIN 80" or "ISOPTIN 120" on one side and with "KNOLL" on the reverse side. Revised August, 1984. 2385

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CME Test #28: Answer Sheet

Effect of Intracoronary Thrombolytic Therapy on Exercise-Induced Ischemia After Acute Myocardial Infarction

Instructions: Mark the appropriate box with an "X."
Test questions appear on page 760.

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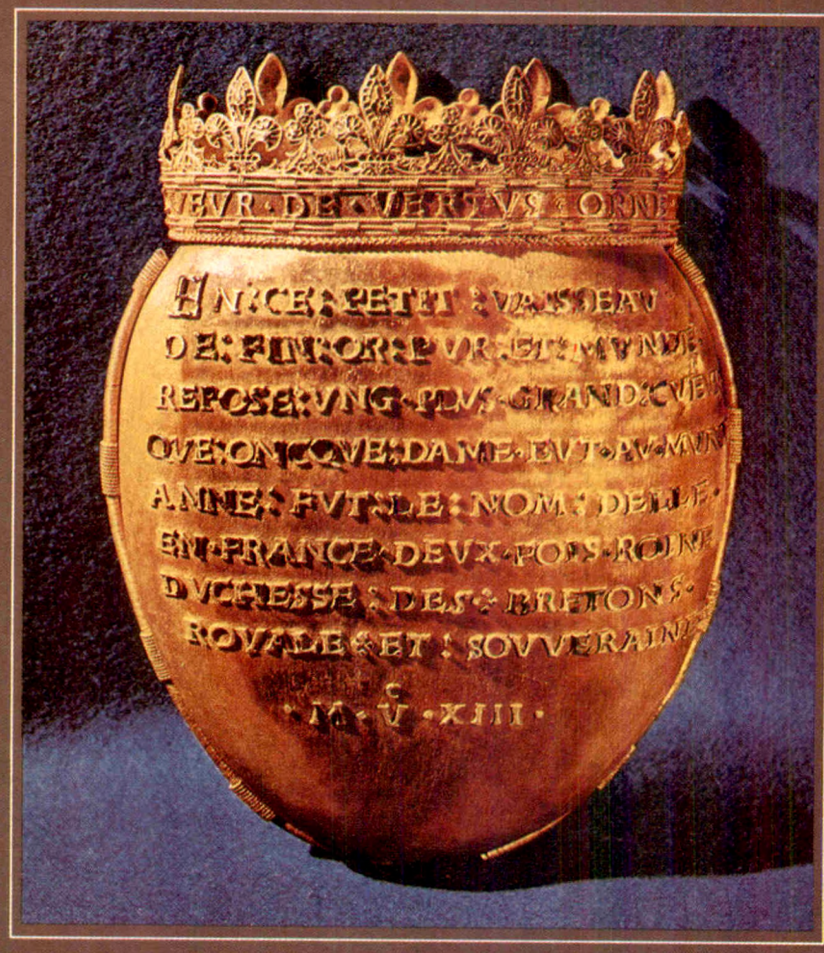

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BRIEF SUMMARY

INDICATIONS—Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency of, or eliminate, anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack. Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.
PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.
ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.
DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25, 50 and 75 mg. For complete details, please see the full prescribing information.

PE 3026 7/84 – 2

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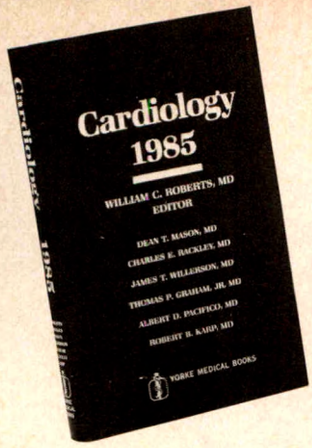

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Clinical Clues to MIXED ANGINA *No. 5*

The stairs seem steeper today

Most days she can climb the stairs with no difficulty. But today she was less than half-way up when an angina attack stopped her.

That's the unpredictability of MIXED ANGINA—vasoconstriction coexisting with fixed coronary lesion, to produce a critical reduction of myocardial blood flow.

And because vasoconstriction is an unpredictable event, ischemia and pain occur unpredictably:

- at varying levels of exercise
- at rest, or even during sleep
- upon exposure to cold
- under emotional stress
- diurnally, typically in the morning

PROCARDIA® (nifedipine) is a primary therapy for the patient with MIXED ANGINA. It prevents vasoconstriction in both large coronary arteries and coronary arterioles to maintain myocardial blood flow and oxygen supply. At the same time, PROCARDIA dilates peripheral arteries to reduce afterload and myocardial oxygen demand.

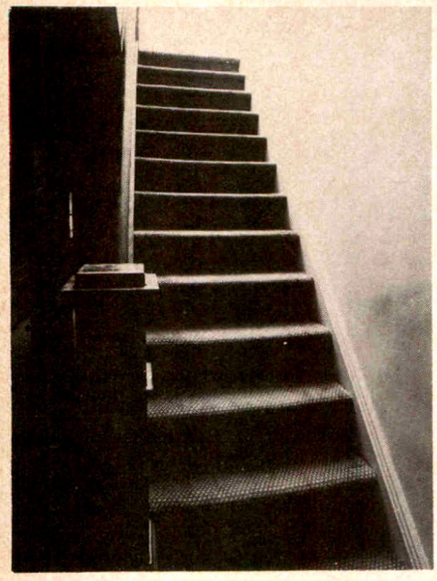
As a result, PROCARDIA can significantly reduce your patient's angina attack rate and need for nitroglycerin.[1]

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Primary Protection in
MIXED ANGINA

Please see PROCARDIA® (nifedipine) brief summary on next page.

The stairs seem steeper today



PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PRIMARY PROTECTION IN MIXED ANGINA

Usual Effective Dosage: 30 to 60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level a a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration o severity of angina on starting PROCARDIA or at the time of dosage increases.

A Favorable Safety Profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

Reference:

1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 106:644-652, 1983.

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA (nifedipine) therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA patients. No clinical significance for these findings has been demonstrated.

Although PROCARDIA has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to PROCARDIA therapy is uncertain in most cases but probable in some.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, or discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80% and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, mice and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cramps, flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, gingival hyperplasia, and erythromelalgia. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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TABLETS
(quinidine polygalacturonate)

INDICATIONS AND USAGE: CARDIOQUIN Tablets are indicated as maintenance therapy after spontaneous and electrical conversion of atrial tachycardia, flutter or fibrillation and in the treatment of premature atrial and ventricular contractions, paroxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, and paroxysmal ventricular tachycardia when not associated with complete heartblock. CONTRAINDICATIONS: History of hypersensitivity to quinidine, complete A-V block, complete bundle branch block or other severe intraventricular conduction defects, myasthenia gravis, arrhythmias associated with digitalis toxicity. WARNINGS: In the treatment of atrial fibrillation with rapid ventricular response, use digitalis to control ventricular rate prior to administration of quinidine. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine. *Potentially toxic digoxin plasma levels may occur when quinidine is administered concurrently. Consider reducing digoxin dosage and monitoring for digitalis toxicity.* Evidence of quinidine cardiotoxicity (increased P-R and Q-T intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia) mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. NOTE: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia. Quinidine should be used with extreme caution in the presence of incomplete A-V block, since complete block and asystole may result. Quinidine may cause abnormalities of rhythm in digitalized patients; therefore, it should be used with caution in the presence of digitalis intoxication. Caution is also called for in patients exhibiting renal, cardiac or hepatic insufficiency because of potential toxic accumulation of quinidine in plasma. PRECAUTIONS: A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncracy to quinidine. ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered. Periodic blood counts and liver and kidney function tests should be performed during long-term therapy.

DRUG INTERACTIONS OF QUINIDINE:

DRUG	EFFECT
With anticholinergic drugs	Additive vagolytic effect.
With cholinergic drugs	Antagonism of cholinergic effects.
With carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine.
With coumarin anticoagulants	Reduction of clotting factor concentrations.
With tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade.
With phenothiazines and reserpine	Additive cardiac depressive effects.
With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine.
With digoxin	Increased plasma concentrations of digoxin (see WARNINGS).

PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: The drug should be used with caution due to excretion of the quinidine in breast milk. ADVERSE REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and/or disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTESTINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricular tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEMATOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing with intense pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Full Prescribing Information.

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NOVEMBER 15, 1985

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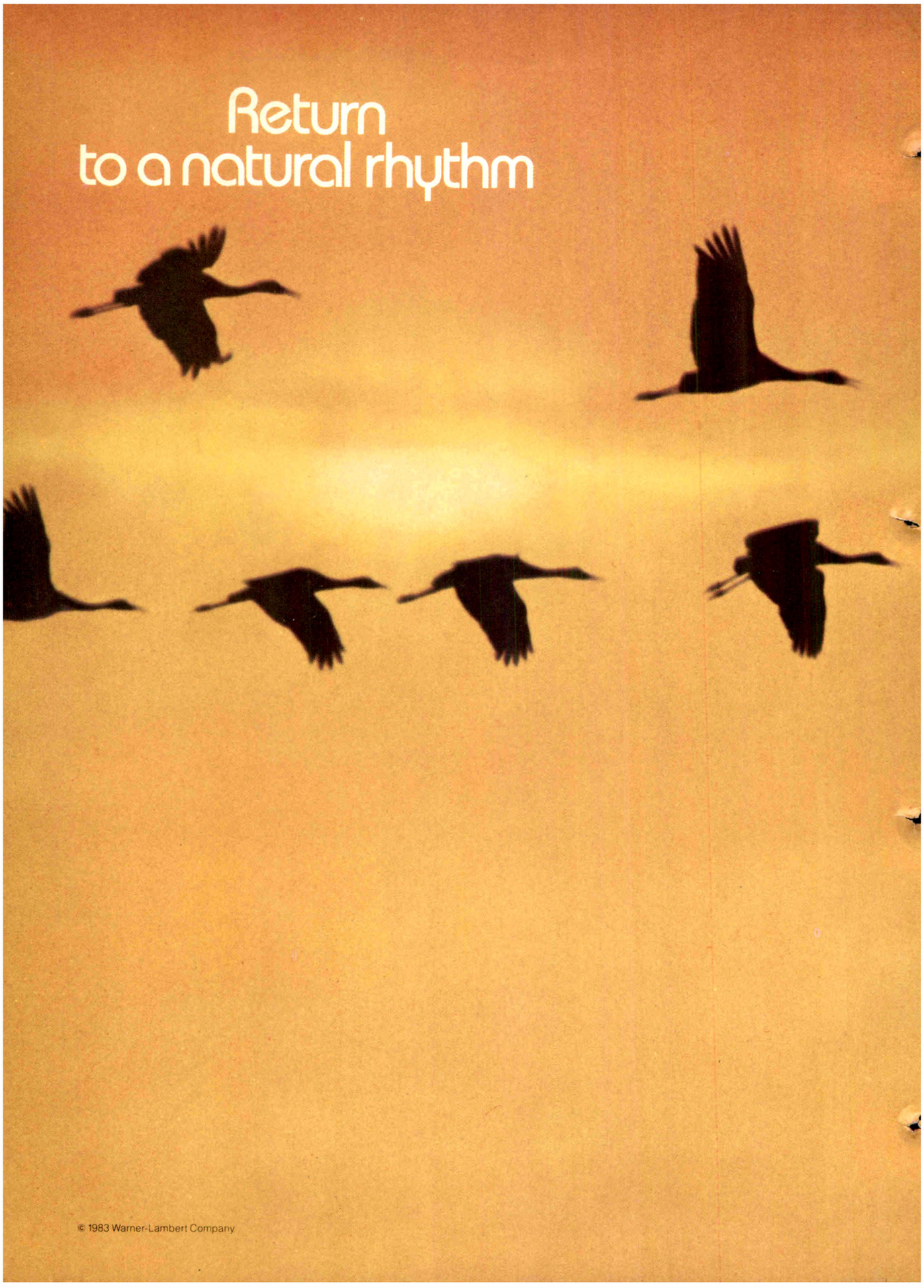

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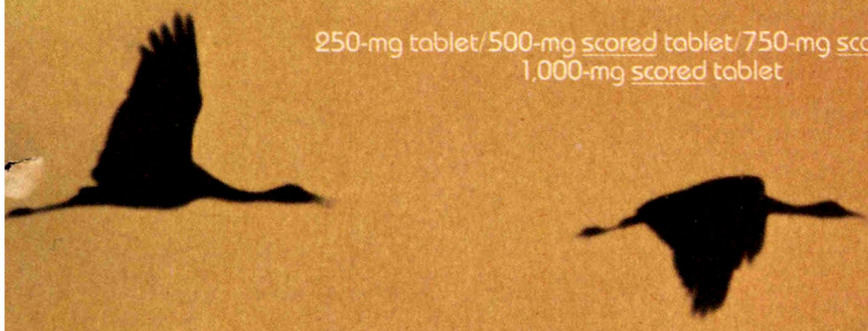

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Please see next page for brief summary of prescribing information.

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Before prescribing, please see full prescribing information.
A Brief Summary follows.

> The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions, ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: Hypersensitivity to procainamide is an absolute contraindication. In this connection, cross-sensitivity to procaine and related drugs must be borne in mind.

Procainamide should not be administered to patients with complete atrioventricular heart block. It is also contraindicated in cases of second degree and third degree A-V nodal block unless an electrical pacemaker is operative.

It has been suggested that procainamide be contraindicated in patients with myasthenia gravis.

WARNINGS: Granulocytopenia may follow the use of procainamide, and deaths from sepsis have occurred. Leukocyte changes are most likely to occur during the first three months of therapy. During this time routine blood counts should be done at least every two weeks, and thereafter at longer intervals throughout maintenance procainamide therapy. Complaints of malaise and aches (a flu-type syndrome) are often reported in association with the granulocyte depression.

Patients should be instructed to report such symptoms promptly, as well as any soreness of mouth, throat or gums, unexplained fever, or symptoms of an upper respiratory tract infection. If these should occur and a complete blood count indicates a granulocyte depression, procainamide therapy should be discontinued immediately and appropriate treatment instituted. Recovery of leukocyte count usually occurs within a few weeks.

The incidence of granulocytopenia appears to be higher with procainamide sustained-release tablets than with standard tablets.

PRECAUTIONS: General—During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Serious hypotension can result from peripheral vasodilation and from decreases in cardiac output. At high plasma levels, procainamide may produce sinus tachycardia due to reflex sympathetic response to its hypotensive effect. Large doses may increase cardiac automaticity and can induce complete atrioventricular block, cardiac standstill, or ventricular extrasystoles that may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram: a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged, and the QRS and T waves show some decrease in voltage.

Antinuclear antibodies (ANA) are often found in patients receiving long-term procainamide therapy. The induction of ANA appears to be independent of dosage. Patients with procainamide-induced increases in ANA titers may develop a syndrome resembling systemic lupus erythematosus (SLE). The mechanism of this syndrome is uncertain. Polyarthralgia, arthritic symptoms, and pleuritic pain are common symptoms; to a lesser extent fever, myalgia, skin lesions, pleural effusion, pericarditis, headache, fatigue, weakness, nausea and abdominal pain may occur. Rare cases of thrombocytopenia, Coombs' positive hemolytic anemia, increased SGOT, SGPT, and serum amylase have been reported which may be related to this SLE-like syndrome.

It is recommended that tests for systemic lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy. The drug should be discontinued if there is a rising ANA titer or clinical symptoms of SLE appear. The SLE-like syndrome may be reversible upon discontinuation of the drug. If discontinuation does not cause remission of the symptoms, corticosteroid therapy may be effective. If the SLE-like syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, corticosteroid suppressive therapy may be used concomitantly with procainamide.

Information for Patient—Practitioners should give the following information and instructions to patients receiving Procan SR.

1. Do not crush or chew these tablets. Swallow them whole.
2. Take this medicine exactly as directed by your doctor. Do not miss any doses and do not take more medicine than ordered. Do not stop taking this medicine without first checking with your doctor.
3. If you miss a dose and remember within one hour or so, take it as soon as possible. Then go back to your regular dosing schedule. Do not take double doses. If you have any questions about this, check with your doctor.
4. Report to your doctor any flu-type symptoms, such as malaise and aches, as well as any soreness of the mouth, throat or gums, unexplained fever, skin rash, unusual bleeding or bruising, symptoms that resemble arthritis, or symptoms of an upper respiratory tract infection.
5. Do not be concerned if you occasionally notice in your stool something that looks like a tablet. In Procan SR (procainamide hydrochloride tablets), the drug is 'held' in a wax core that has been specially designed to slowly release the drug for your body to absorb. When this process is completed the empty, nonabsorbable wax core, which looks nearly unchanged, is eliminated from your body.
6. Keep container tightly closed and store in a cool, dry place.

Laboratory Tests—Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals.

Routine blood counts are advisable during maintenance procainamide therapy. See WARNINGS for additional information.

Plasma concentrations of procainamide and NAPA should be monitored in patients with renal disease, hepatic disease, cardiac failure, or low cardiac output states.

Drug Interactions

1. **Antiarrhythmics:** Concurrent use with procainamide may result in additive cardiac effects and/or additive toxic effects.
2. **Anticholinergics:** Procainamide enhances the anticholinergic effects. Extreme caution must be exercised with such a combination.
3. **Anticholinesterases:** Procainamide antagonizes the effect of anticholinesterases in myasthenia gravis, and paralysis returns.
4. **Antihypertensives:** Procainamide may potentiate the hypotensive effects of thiazide diuretics and other antihypertensive agents. Adjustment of dosage may be required.
5. **Cimetidine:** It has been reported that the histamine H_2-antagonist cimetidine reduces renal clearance of procainamide and NAPA, resulting in higher plasma concentrations for longer durations. Caution should be exercised when administering these drugs concurrently, especially in the elderly, who have a reduced ability to clear all three. Dosage modification may be required.
6. **Neuromuscular Blocking Agents:** Procainamide potentiates the effects of skeletal muscle relaxants such as succinylcholine. It also may enhance or prolong the neuromuscular blocking activity of bacitracin, colistimethate, dihydrostreptomycin, gentamicin, gramicidin, kanamycin, neomycin, polymyxin B, streptomycin, and viomycin, producing respiratory depression.

Pregnancy—Pregnancy Category C. Animal reproduction studies have not been conducted with procainamide. It is also not known whether procainamide can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Procainamide should be given to a pregnant woman only if clearly needed.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when procainamide is administered to a nursing woman.

ADVERSE REACTIONS: Most frequent, especially with large oral doses:
1. Anorexia 2. Nausea 3. Vomiting 4. Diarrhea 5. Urticaria 6. Pruritus.

Less frequent: 1. Reactions in patients on long-term procainamide therapy: a. Antinuclear antibodies (ANA) b. Syndrome resembling systemic lupus erythematosus (SLE) (See PRECAUTIONS).

2. Hypersensitivity reactions: a. Angioneurotic edema b. Maculopapular rash c. Fever d. Eosinophilia e. Hypergammaglobulinemia.

Infrequent: 1. Granulocytopenia, sometimes resulting in death (See WARNINGS) 2. Convulsions 3. Psychosis with hallucinations 4. Confusion 5. Mental depression 6. Giddiness 7. Lightheadedness 8. Weakness 9. Bitter taste.

Rare: 1. Hypotension 2. A case was reported with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following a single dose of the drug.

OVERDOSAGE: Signs and symptoms of overdosage of procainamide include severe hypotension, ventricular fibrillation, widening of the QRS complex, junctional tachycardia, intraventricular conduction delay, oliguria, lethargy, confusion, nausea, and vomiting.

If ingestion is recent, gastric lavage or emesis may reduce absorption. Dopamine, phenylephrine or levarterenol may be helpful in reversing severe hypotensive responses.

Management of overdosage includes symptomatic treatment with ECG and blood pressure monitoring. Procainamide toxicity can usually be treated, if necessary, by administering vasopressors after adequate fluid volume replacement. Intravenous infusion of 1/6 molar sodium lactate injection reportedly reduces the cardiotoxic effects of procainamide.

The urinary elimination of procainamide is proportional to the glomerular filtration rate but is also affected by changes in urinary pH. Procainamide is relatively lipid-soluble as a free base, but the ionized form is not. Acid urine, therefore, leads to ion trapping of procainamide which enters the urine by passive diffusion from the plasma. Accordingly, renal clearance of procainamide can be considerably increased by maintaining a low urinary pH and high flow rates.

If procainamide toxicity causes severe hypotension and renal insufficiency, urinary elimination of procainamide and NAPA is decreased, and hemodialysis may be required. Hemodialysis significantly reduces the serum half-life of procainamide, and effectively removes procainamide and NAPA. Peritoneal dialysis is not effective.

It has been reported that one patient who ingested approximately 7 grams of procainamide hydrochloride recovered after treatment consisting of IV levarterenol, IV furosemide, attempted volume expansion with albumin, and hemodialysis. Also reported is the case of an elderly patient who recovered after ingestion of approximately 19 grams of procainamide hydrochloride. The patient was treated with IV isoproterenol and IV epinephrine. The latter report suggested that insertion of a ventricular pacing electrode is a reasonable precautionary measure in case high grade A-V block develops.

Storage Conditions—Protect from moisture. Store bottles below 30° C (86° F). Store unit-dose packages at controlled room temperature, 15°-30° C (59°-86° F). 0207G012
Caution: Federal law prohibits dispensing without prescription.

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†CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs (e.g., procainamide) known to affect the white cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. See INDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Neutropenia/Agranulocytosis—Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria—Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure $>20\%$ were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine $>20\%$ above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C—There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis have occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets.
(J3-658C)

Reference: 1. Cannon PJ, Criley JM, Dzau VJ, et al: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Col Cardiol 2:755–763, 1983.

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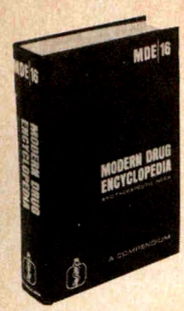

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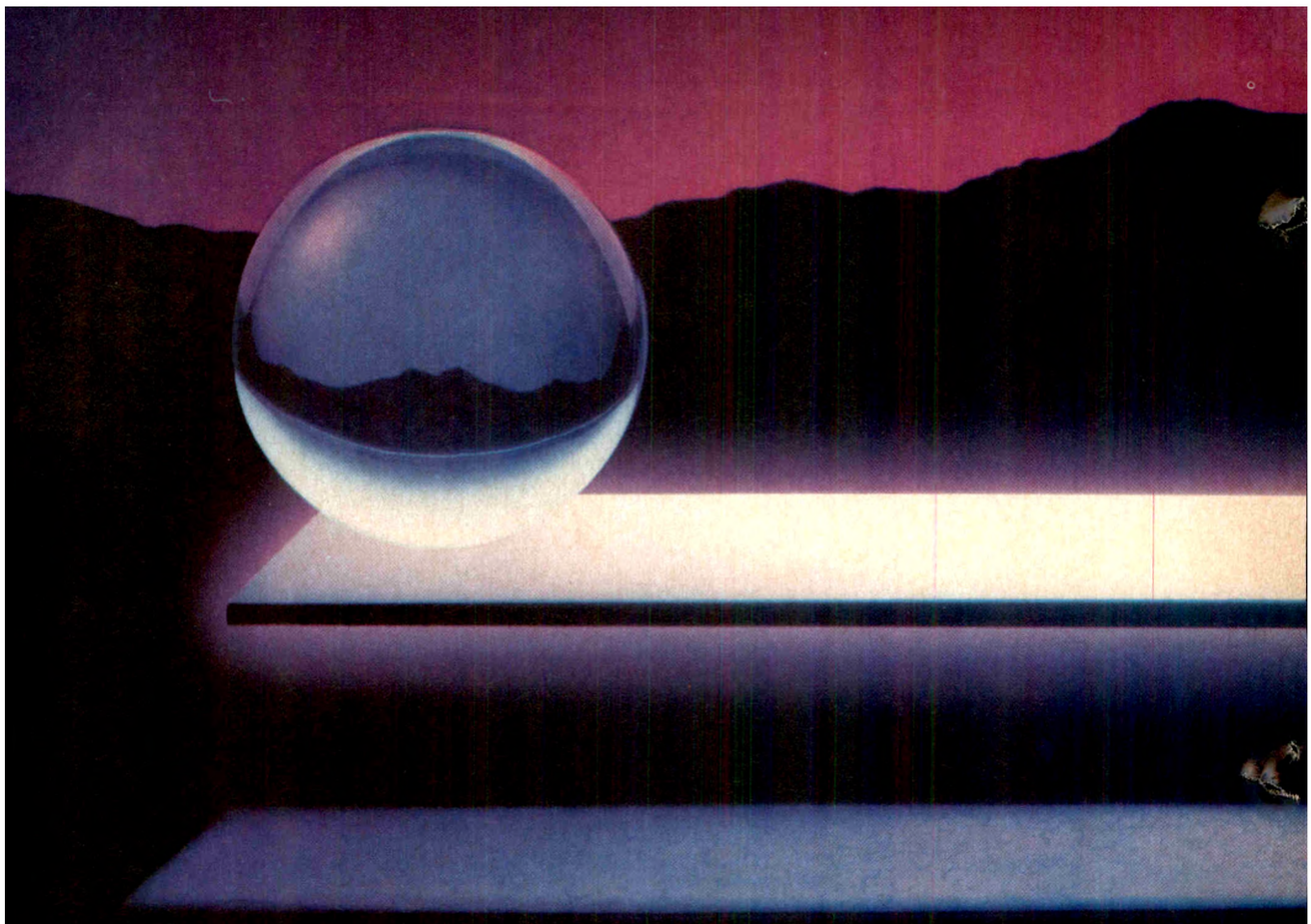

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- Has a side effects profile similar to placebo and no significant abnormalities in clinical/laboratory evaluations
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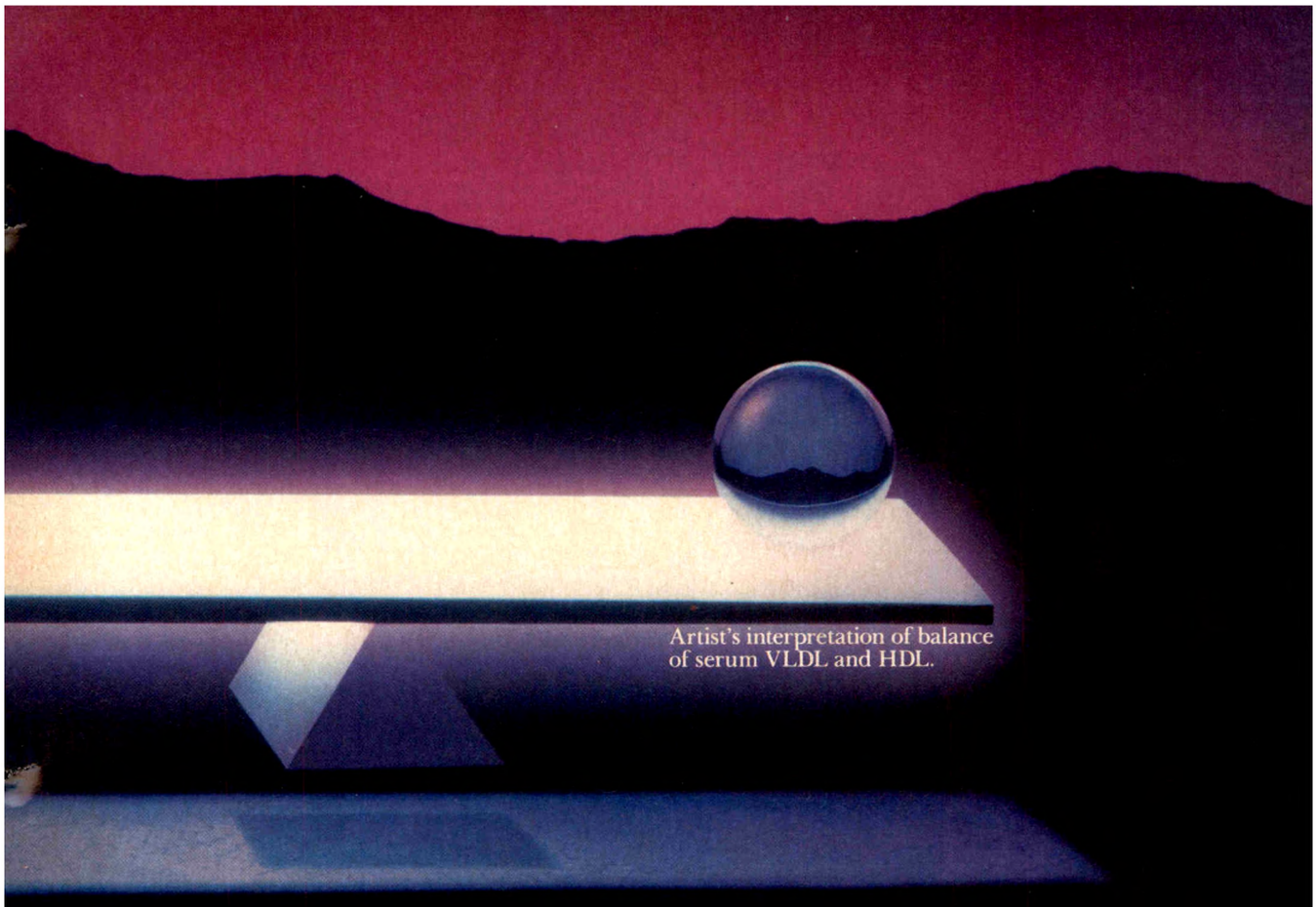
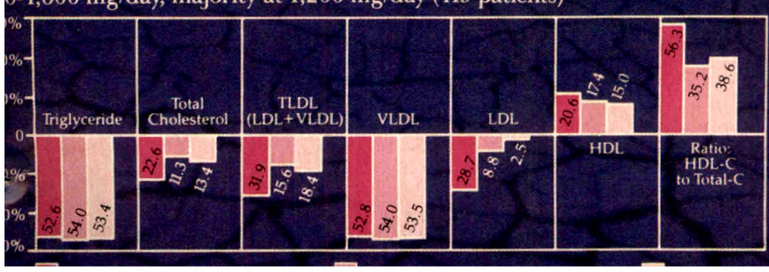


Artist's interpretation of balance of serum VLDL and HDL.

o Therapy of Certain Dyslipidemias

Lipid-regulating efficacy: pen-label phase of US multicenter study t end of 12 lunar months*[1]

erage percent change from baseline at doses ranging from 0-1,600 mg/day, majority at 1,200 mg/day (119 patients)†



Diet, exercise and weight loss are the first choice in therapy of lipid disorders.

*Visit every 4 weeks during long-term use of LOPID.

†Data cited on this graph reflect clinical experience based on the multicenter trial. They do not imply an indication for Types IIa and IIb dyslipidemias.

1. Data on file, Medical Affairs Dept, Parke-Davis.

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Please see following page for brief summary of prescribing information.

TWO-WAY LIPID REGULATOR

LOPID®

(gemfibrozil capsules, USP) 300 mg

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. In addition, LOPID may increase the high density lipoprotein (HDL) cholesterol fraction, an action considered of possible benefit to inhibition of the atherosclerotic process.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID also inhibits synthesis of VLDL carrier apoprotein, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, primarily as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO
		Total	VLDL	LDL	HDL	HDL Cholesterol / Total Cholesterol
IIa	−44%	−4.2%	−44.3%	− 5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	− 6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk.

LOPID (gemfibrozil capsules, USP) has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. However, it must be understood that there is no evidence that use of any lipid-altering drug will be beneficial in preventing death from coronary heart disease (see WARNINGS). Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of drug-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings.)

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies: Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID (gemfibrozil capsules, USP) therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Seasonal Variation of Lipid Levels**—LOPID is not expected to alter seasonal variations of higher serum lipid values in mid-winter and late summer or the lower values in fall and spring.

4. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in female or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Cardiac Arrhythmias**—Although no clinically significant abnormalities occurred that could be attributed to LOPID, the possibility exists that such abnormalities may occur.

10. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria
Central Nervous System: headache, dizziness, blurred vision
Musculoskeletal: painful extremities
Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia
Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints
Central Nervous System: vertigo, insomnia, paresthesia, tinnitus
Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)
Miscellaneous: fatigue, malaise, syncope

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meals. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID (GEMFIBROZIL CAPSULES, USP). THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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CONTENTS

CORONARY HEART DISEASE

839 **Prediction of Functional Capacity and Use of Exercise Testing for Predicting Risk After Acute Myocardial Infarction**

ERLING BIRK MADSEN, ELIZABETH GILPIN, STAFFAN AHNVE, HARTMUT HENNING, and JOHN ROSS, Jr.

Among 1,469 patients discharged after acute myocardial infarction (AMI), 466 patients (32%) underwent treadmill exercise testing close to the time of discharge. An ischemic exercise test response (ST-segment depression or angina) could not be predicted from historical or clinical variables. Good functional capacity (more than 4 METs) could be predicted using age and resting ST-segment changes, and among patients predicted to have a functional capacity of more than 4 METs, only 15% actually experienced low functional capacity on testing. Multivariate analysis of exercise test variables for predicting risk within 1 year selected only functional capacity, and this variable identified a large group of patients (72%) with very low risk of death and new AMI (less than 2%) and a high risk group of patients (29%) with 18% risk of death or new AMI.

846 **Repeated Quantitative Angiograms in Coronary Arterial Aneurysm in Kawasaki Disease**

HIROYUKI NAKANO, KEN UEDA, AKIHIRO SAITO, and KEIKO NOJIMA

To adequately manage patients with Kawasaki disease, the extent of associated coronary aneurysms was classified as follows: grade 0—no significant enlargement of the coronary artery; grade I—localized coronary aneurysms, with a maximum diameter of less than 4.0 mm; grade II—moderate-sized aneurysms, with a maximal diameter between 4.0 and 8.0 mm; and grade III—giant coronary aneurysms, with the maximal diameter greater than 8.0 mm. Most mild coronary aneurysms regressed to normal within a short time. The course of grade II aneurysms varied, depending on initial angiographic coronary size, but they eventually became reduced in size. In contrast, grade III aneurysms usually progressed into obstructive or stenotic coronary lesions. The current grading of severity of coronary artery disease may provide useful criteria to predict the prognosis of patients with Kawasaki disease.

852 **Identification of Best Electrocardiographic Leads for Diagnosing Myocardial Infarction by Statistical Analysis of Body Surface Potential Maps**

FRED KORNREICH, PENTTI M. RAUTAHARJU, JAMES WARREN, TERRENCE J. MONTAGUE, and B. MILAN HORACEK

A critical practical problem in body surface potential map analysis is the selection of optimal subsets of leads and features for diagnostic classification. Multivariate analysis was performed on 120-lead data from 184 normal subjects and 177 patients with myocardial infarction in order to identify leads and features for optimal diagnostic classification. Several areas on the map, most of which were located outside the precordial region, contained leads with important discriminant features. Six features (mostly ST-T measurements) from 3 locations—right subclavicular area, left posterior axillary region and left leg—correctly identified 95% of normal subjects and 95% of patients with myocardial infarction. The same number of features from the standard 12-lead electrocardiogram yielded 95% and 88%, respectively. It is concluded that leads outside the conventional chest locations contain important diagnostic information that can be extracted by the presented method.

857 **Assessment of Left Ventricular Aneurysm Resectability by Two-Dimensional Echocardiography**

CEES A. VISSER, GERARD KAN, RICHARD S. MELTZER, AD C. MOULIJN, GEORGE K. DAVID, and AREND J. DUNNING, *With the technical assistance of* MARGA van CORLER *and* HARRY de KONING

Two-dimensional echocardiography was performed in 56 patients undergoing aneurysmectomy to determine an index of the nonaneurysmal or residual myocardium. The end-diastolic length of normally moving endocardium of the 2 opposite walls in the apical 2- and 4-chamber view, and apical long-axis view was expressed as a fraction

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of the end-diastolic length of the left ventricle. The index was assessed by averaging the 6 ratios obtained. With 1 exception, this index sharply separated survivors from nonsurvivors. The lower limit to survive aneurysmectomy was 40%.

861 **Relation Between Heart Rate and QT Interval in Exercise-Induced Myocardial Ischemia**

MASSIMO ROMANO, TERESA Di MARO, GIOVANNI CARELLA, MARIA ROSARIA COTECCHIA, GIUSEPPE FERRO, and MASSIMO CHIARIELLO

The relation between heart rate and QT interval during dynamic upright exercise was assessed in 18 control subjects and in 23 patients with coronary stenoses and exercise-induced myocardial ischemia. A significant negative linear correlation was found in both groups; the correlation coefficient was higher in control subjects than in the group with coronary artery disease (CAD) ($r = -0.78$ and -0.64, respectively), probably as a consequence of the nonhomogeneous response in CAD patients. The regression line had a flatter slope in patients with CAD, whereas a faster decrease of the QT increasing rate was seen in control subjects. This phenomenon may be related to an impairment of ischemic myocardium in responding to exercise-induced catecholamine release or to a direct effect of exercise-induced ischemic prolongation of myocardial tension.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

863 **Effects of Oral Amiodarone on Rate-Dependent Changes in Refractoriness in Patients with Wolff-Parkinson-White Syndrome**

PEDRO BRUGADA and HEIN J.J. WELLENS

The effects of oral amiodarone on rate-dependent behavior of the refractory periods during cardiac pacing were studied in 13 patients with the Wolff-Parkinson-White syndrome. Amiodarone produced a rate-dependent increase in refractoriness of the accessory pathway in anterograde direction in 5 patients and in retrograde direction in 3. The right atrial and right ventricular refractory periods continued to shorten significantly when the pacing rate was increased after amiodarone treatment. When these data were correlated with the mode of initiation and termination of tachycardia, a possible effect of the rate-dependent increase in refractoriness of the accessory pathway was observed in only 1 patient. Antiarrhythmic drugs should, ideally, produce a rate-dependent increase in refractoriness in reentrant circuits. This would facilitate prompt spontaneous termination of tachycardia by creating block for the circulating impulse. Further development of new antiarrhythmic drugs should include a search for components resulting in a reliable and predictable rate-dependent increase in refractoriness.

867 **Evaluation by Serial Electrophysiologic Studies of an Abbreviated Oral Loading Regimen of Amiodarone**

ELEANOR E. KENNEDY, LYNDA E. ROSENFELD, CRAIG A. McPHERSON, and WILLIAM P. BATSFORD

Serial evaluation of electrophysiologic variables was used in 25 patients with ventricular tachycardia (VT) to assess the adequacy of a 1-week oral loading regimen at 1,200 mg/day and to modify discharge dosing. During the initial week of loading, highly significant ($p < 0.001$) increases occurred in the AH interval, HV interval, AV nodal Wenckebach cycle length, ventricular refractory period and VT cycle length. After 2 months of maintenance therapy at 800 mg/day or less, as guided by electrophysiologic assessment, there was no additional change in any of the above variables except for an increase in VT cycle length. VT inducibility was not consistently affected. It is concluded that patients can be discharged after 1 week of oral amiodarone loading at 1,200 mg/day, and that modification of maintenance dosing by electrophysiologic assessment fosters steady perpetuation of cardiac amiodarone effect.

872 **Spontaneous Termination of Reciprocating Tachycardia Owing to Interaction of Dual Atrioventricular Nodal Pathways in Patients with an Accessory Pathway**

KARL-HEINZ KUCK, KLAUS-PETER KUNZE, MICHAEL SCHLÜTER, and WALTER BLEIFELD

In 7 of 125 patients with accessory atrioventricular (AV) pathways, the presence of dual AV nodal pathways was suggested by the mode of spontaneous termination of reciprocating tachycardia. Three types of tachycardia termination were observed. In 2 patients with antidromic tachycardia, termination was a result of AV nodal reentry. In 3 other patients with antidromic tachycardia, termination occurred after a sudden switch from a slow to a fast AV nodal pathway, resulting in conduction block within the AV reentrant circuit. In 2 patients with orthodromic tachycardia, termination was caused by the occurrence of an AV nodal echo beat. The interaction of dual AV nodal pathways within the reentrant circuit incorporating the accessory pathway always inhibited sustained reciprocating tachycardia.

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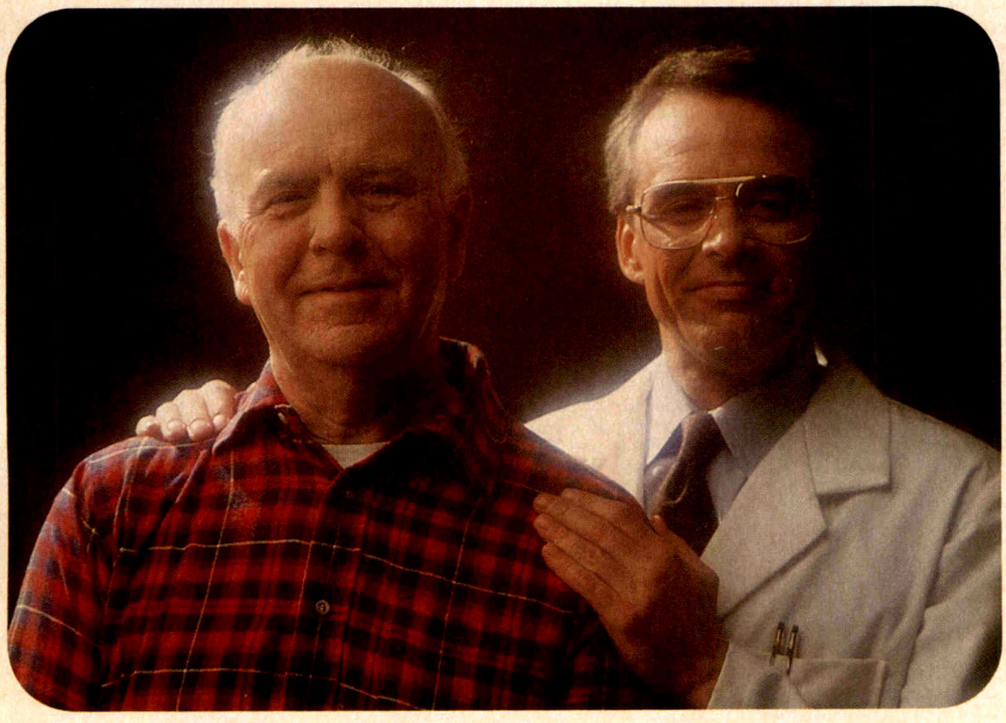

- Many common prescription and OTC drugs can cause variations in digoxin absorption.
- Lanoxicaps are more rapidly and completely absorbed to minimize these interactions.
- Less variability in absorption means less risk of over- or under-digitalization, and increased safety.

LANOXICAPS®

(digoxin solution in capsules)

0.05 mg, 0.1 mg, 0.2 mg strengths

The new standard in digoxin delivery

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Please see brief summary of prescribing information on next page.

84LN

LANOXICAPS®
(digoxin solution in capsules)

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LANOXICAPS®
(digoxin solution in capsules)
50 μg (0.05 mg) I.D. Imprint A2C (red)
100 μg (0.1 mg) I.D. Imprint B2C (yellow)
200 μg (0.2 mg) I.D. Imprint C2C (green)

Brief Summary of Prescribing Information

Before using Lanoxicaps® (digoxin solution in capsules), the physician should be thoroughly familiar with the basic pharmacology of this drug as well as its drug interactions and its indications and usage.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in ventricular fibrillation. Any untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS: The use of digoxin or other digitalis glycosides in the treatment of obesity is unwarranted and dangerous.

It is recommended that digoxin in soft capsules be administered in divided daily doses to minimize any potential adverse reactions. Where compliance is considered a problem, single daily dosing may be appropriate (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section in complete prescribing information).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary. Careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS:

General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section in complete prescribing information). More time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range", because potassium depletion sensitizes the myocardium to digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section in complete prescribing information).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. Hypocalcemia can nullify the effects of digoxin in man; digoxin may be ineffective until serum calcium is restored to normal.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine and verapamil cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized.

Certain antibiotics may increase digoxin absorption in patients who convert digoxin to inactive metabolites in the gut (see Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section in complete prescribing information). The magnitude of rise in serum digoxin concentration may be as much as two-fold in some cases. This interaction is significantly reduced if digoxin is given as Lanoxicaps.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g. hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e. Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sino-atrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias. *Quinidine* and *verapamil* cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain *antibiotics* increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids kaolin-pectin, sulfasalazine, neomycin, cholestyramine* and certain *anticancer drugs* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. *Thyroid* administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although β adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% being considered serious (1 to 4% of patients receiving digoxin). Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:

Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease. Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage. Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances.

Gastrointestinal—Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdosage. Uncontrolled heart failure may also produce such symptoms.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, apathy and psychosis can occur.

Other—Gynecomastia is occasionally observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

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CONTENTS

877 Electrophysiologic Evaluation of the Antiarrhythmic Effects of N-Acetylprocainamide for Ventricular Tachycardia Secondary to Coronary Artery Disease

JONATHAN WYNN, DENNIS S. MIURA, VILMA TORRES, DAVID FLOWERS, DEBORAH KEEFE, SHARON WILLIAMS, and JOHN C. SOMBERG

N-acetylprocainamide (NAPA), an active antiarrhythmic metabolite of procainamide, was studied in 12 patients with coronary artery disease who presented with a cardiac arrest or documented sustained ventricular tachycardia (VT). Programmed electrical stimulation studies were performed in all 13 patients and all had inducible VT. Procainamide, 1,000 mg administered intravenously, was tested in 10 patients, and in 8 of them VT could still be provoked. NAPA, 18 mg/kg intravenously, prevented VT induction in 5 of 12 patients. Two patients have done well with long-term oral NAPA therapy, 1 died shortly after hospital discharge, and 2 patients had VT during Holter monitoring early in the therapeutic program. NAPA may be a useful antiarrhythmic drug for patients with VT.

883 Electropharmacologic Testing in Sustained Ventricular Tachycardia Associated with Coronary Heart Disease: Value of the Response to Intravenous Procainamide in Predicting the Response to Oral Procainamide and Oral Quinidine Treatment

DANIEL S. OSERAN, ELI S. GANG, MARK E. ROSENTHAL, WILLIAM J. MANDEL, and THOMAS PETER

Twenty patients with inducible sustained ventricular tachycardia were prospectively evaluated in order to determine whether the response to intravenous procainamide, as assessed by programmed ventricular stimulation, predicted the response to oral procainamide and oral quinidine administration. Overall, 6 patients (30%) responded favorably to intravenous procainamide, 10 (50%) responded to oral quinidine and 5 (25%) responded to oral procainamide. Fifteen patients (75%) had a concordant drug response for intravenous and oral procainamide. Ten patients (50%) had a concordant response for intravenous procainamide and oral quinidine. Fifteen patients (75%) had a concordant response for oral procainamide and oral quinidine. Thus, in patients with sustained ventricular tachycardia, the response to intravenous procainamide does not reliably predict the response to oral quinidine or oral procainamide. Serial day drug studies with these agents appear to be necessary.

887 Spectrum of Antiarrhythmic Response to Encainide

HENRY J. DUFF, DAN M. RODEN, EDMUND L. CAREY, THEODORE WANG, R. KIRBY PRIMM, and RAYMOND L. WOOSLEY

Thirty-seven patients were treated with encainide. Eight patients with sustained ventricular tachycardia and ischemic heart disease did not respond favorably to encainide, and more important, they frequently had paradoxical worsening of arrhythmias on encainide. In contrast, encainide was highly effective in patients with sustained ventricular tachycardia in the absence of old myocardial infarction. In patients with symptomatic, nonsustained ventricular tachycardia, encainide was also frequently effective independent of the underlying heart disease.

892 Exercise-Induced Left Bundle Branch Block and Its Relation to Coronary Artery Disease

CHARLES VASEY, JACQUELINE O'DONNELL, STEPHEN MORRIS, and PAUL McHENRY

The records of 2,584 consecutive patients who underwent both treadmill exercise testing and coronary cineangiography were reviewed to detemine the relation between exercise-induced, acceleration-dependent left bundle branch block (LBBB) and the presence of coronary artery disease (CAD). Rate-dependent LBBB during exercise was identified in 28 patients (1.1%), who were categorized according to their presenting symptoms. CAD was present in 7 of 10 patients who presented with classic angina pectoris, but 12 of 13 patients presenting with atypical chest pain had normal coronary arteries. All 10 patients in whom LBBB developed at a heart rate of 125 beats/min or greater were free of CAD. It is concluded that patients presenting with atypical chest pain in whom rate-dependent LBBB develops during treadmill exercise testing are significantly less likely to have CAD than patients who present with classic angina, and the onset of LBBB at a heart rate of 125 beats/min or greater is highly correlated with the presence of normal coronary arteries, regardless of patient presentation.

CONGESTIVE HEART FAILURE

896 Acute Effects of Digoxin on Total Systemic Vascular Resistance in Congestive Heart Failure Due to Dilated Cardiomyopathy: A Hemodynamic-Hormonal Study

HILLEL S. RIBNER, DOMINIC A. PLUCINSKI, ANN-MING HSIEH, DENNIS BRESNAHAN, AGOSTINO MOLTENI, JOSEPH ASKENAZI, and MICHAEL LESCH

The effects of the digitalis glycosides on systemic vascular resistance (SVR) in patients with congestive heart failure are controversial. Most investigators report a reduction in total SVR, which has been ascribed to withdrawal of elevated sympathetic tone. However, a decrease in SVR has not been found in all cases; plasma

Continued on page A16

norepinephrine levels have not previously been measured; and the roles of the renin-angiotensin-aldosterone and vasopressin systems are not known. Therefore, hemodynamic and hormonal changes were correlated after the intravenous administration of 1.0 mg of digoxin to 11 normotensive men in sinus rhythm with congestive heart failure due to dilated cardiomyopathy. Although significant decreases occurred in both plasma renin activity and plasma norepinephrine levels, total SVR did not decrease. Accordingly, improvement in cardiac function in this group appears to be a result of enhanced contractility without an associated reduction in impedance. Lack of concordance between SVR and changes in vasoactive hormones remains to be explained.

CONGENITAL HEART DISEASE

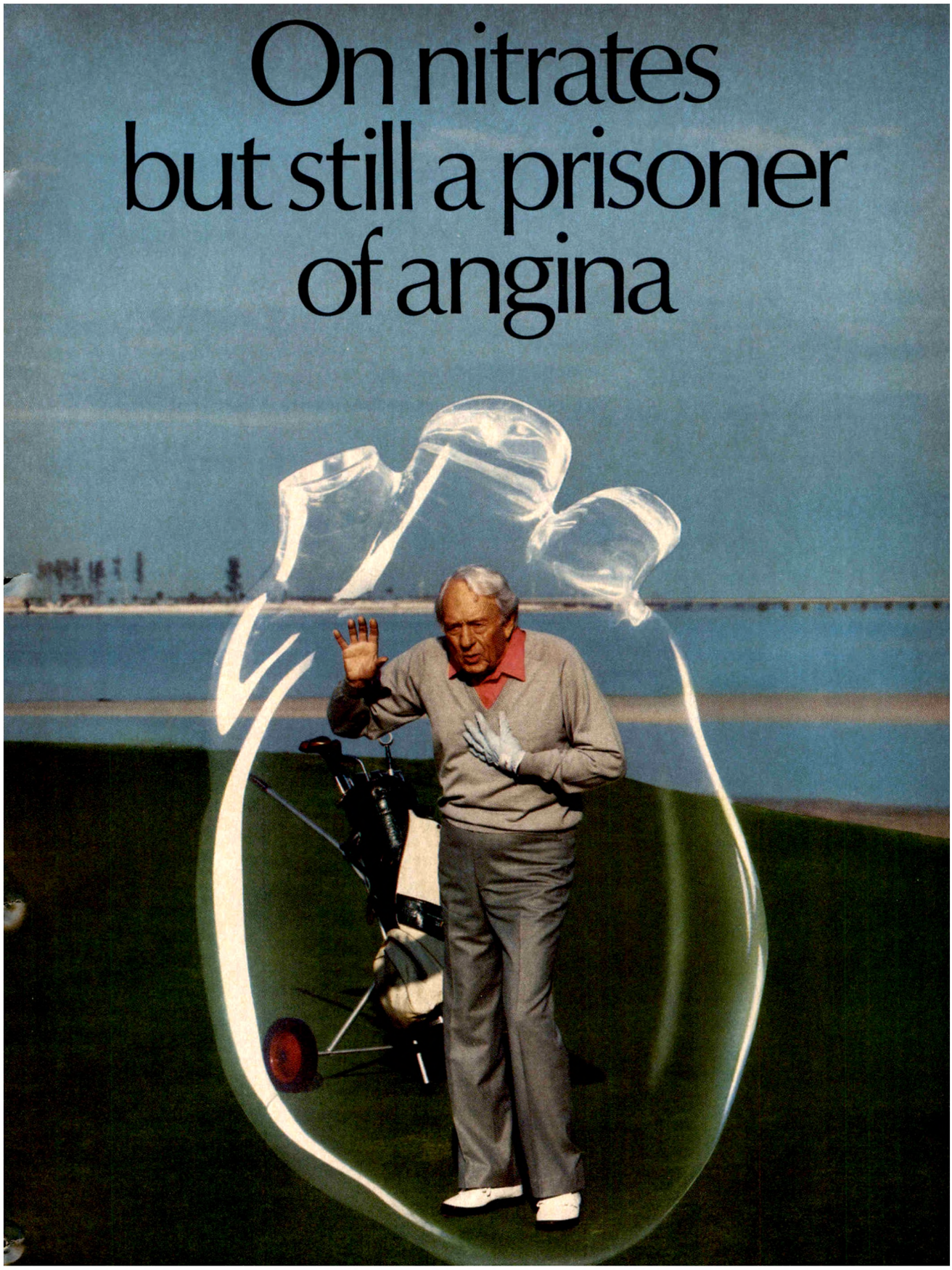
905 Response to the Valsalva Maneuver After the Fontan Procedure for Tricuspid Valve Atresia, Single Ventricle or Pulmonic Valve Atresia

SAMUEL S. GIDDING, AMNON ROSENTHAL, ALBERT P. ROCCHINI, and MACDONALD DICK

Valsalva maneuvers were performed during cardiac catheterization in 9 patients who had undergone a Fontan operation and in 10 control subjects. Patients in the Fontan group had higher right atrial pressure, lower cardiac index, lower stroke index and higher systemic vascular resistance than control subjects. Four Fontan patients had a normal 4-phase Valsalva response and 5 did not. Right atrial pressure was similar in normal and abnormal responders, whereas in the normal responders cardiac index and stroke index were higher and systemic vascular resistance was lower. Thus, cardiac output is a better predictor of a normal response to the Valsalva maneuver than right atrial pressure in patients after the Fontan procedure. A normal response to the supine Valsalva maneuver suggests a cardiac index greater than 2.4 liters/min/m^2 and stroke index greater than 31 ml/beat/m^2.

910 LETTERS

INSTRUCTIONS TO AUTHORS on page 882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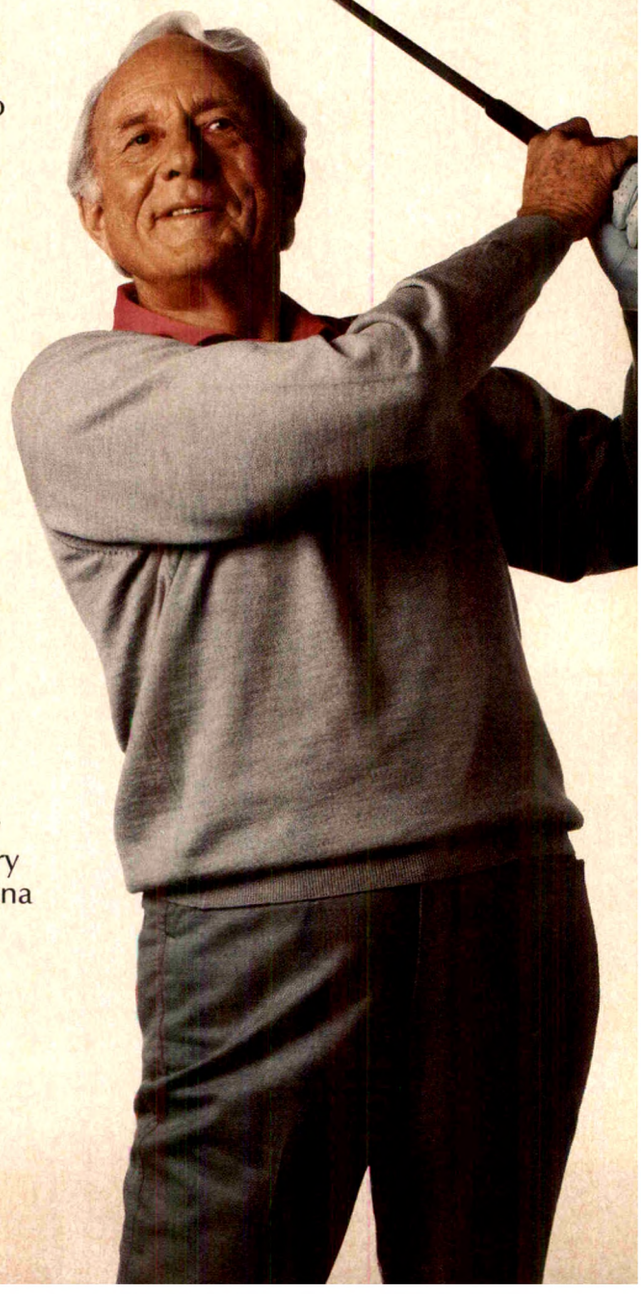

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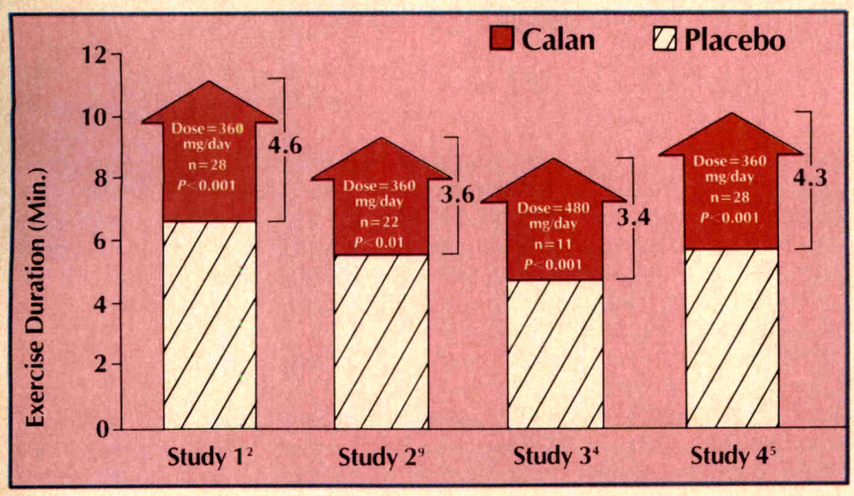

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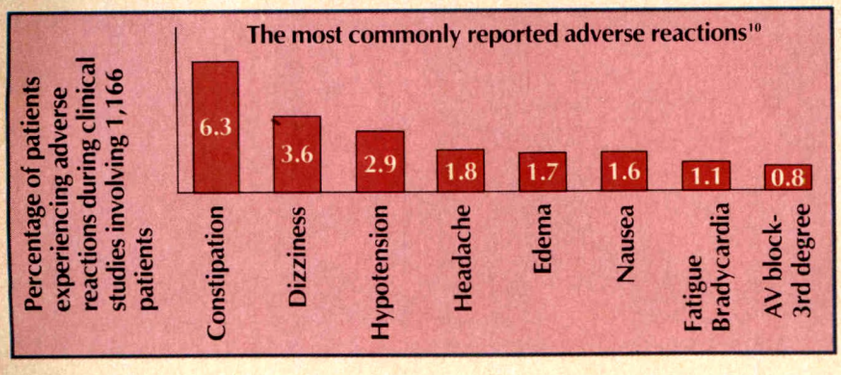

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In one study involving 63 patients "verapamil therapy was not discontinued in any patient because of the development of adverse reactions."[8]

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References:

1. Hillis, D., in Hillis, D. (Moderator); Frishman, W.; Leon, M.; Packer, M.; Robertson, R. M.; Subramanian, B., and Winniford, M. (Discussants): The Expanding Role of Calcium Channel Blockers, 1984. **2.** Subramanian, B., and others: Long-Term Antianginal Action of Verapamil Assessed with Quantitated Serial Treadmill Stress Testing, Am. J. Cardiol. *48*: 529-535 (Sept.) 1981. **3.** Subramanian, B.: Long-Term Therapy of Angina with Calcium Antagonists, Cardiovasc. Rev. Rep. *4*:493-497 (April) 1983. **4.** Leon, M.B.: Combination Therapy Using Calcium-Channel Blockers and Beta Blockers in Patients with Chronic Stable Angina Pectoris, Cardiovasc. Rev. Rep. *4*:171-177 (Feb.) 1983. **5.** Subramanian, V. B., and others: Rationale for the Choice of Calcium Antagonists in Chronic Stable Angina: An Objective Double-Blind Placebo-Controlled Comparison of Nifedipine and Verapamil, Am. J. Cardiol. *50*:1173-1179 (Nov.) 1982. **6.** Weiner, D. A., and others: Efficacy and Safety of Verapamil in Patients With Angina Pectoris After 1 Year of Continuous, High-Dose Therapy, Am. J. Cardiol. *51*:1251-1255 (May 1) 1983. **7.** Frishman, W. H., and others: Superiority of Verapamil to Propranolol in Stable Angina Pectoris: A Double-blind, Randomized Crossover Trial, Circulation *65* (Suppl. 1):51-59 (Jan.) 1982. **8.** Scheidt, S., and others: Long-Term Effectiveness of Verapamil in Stable and Unstable Angina Pectoris: One-Year Follow-Up of Patients Treated in Placebo-Controlled Double-Blind Randomized Clinical Trials, Am. J. Cardiol. *50*:1185-1190 (Nov.) 1982. **9.** Bowles, M. J., and others: Double-blind Randomized Crossover Trial of Verapamil and Propranolol in Chronic Stable Angina, Am. Heart J. *106*:1297-1306 (Dec.) 1983. **10.** Product Labeling.

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Adverse Reactions: Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in less than 0.5% of patients, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions, spotty menstruation, ecchymosis, bruising, gynecomastia, and psychotic symptoms. Overall continuation rate was 94.5% in 1,166 patients.

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CORONARY HEART DISEASE

Prediction of Functional Capacity and Use of Exercise Testing for Predicting Risk After Acute Myocardial Infarction

ERLING BIRK MADSEN, MD, PhD, ELIZABETH GILPIN, MS, STAFFAN AHNVE, MD, HARTMUT HENNING, MD, and JOHN ROSS, Jr., MD

This study evaluated whether an ischemic exercise test response or functional capacity could be predicted from data available during hospitalization in patients discharged after acute myocardial infarction (AMI). The value of exercise test variables for predicting death and new AMI within 1 year was also examined. Among 1,469 patients, 466 (32%) underwent treadmill exercise testing around the time of discharge. An ischemic exercise test response (ST-segment depression or angina) could not be predicted. Good functional capacity (more than 4 METs) could be predicted from age and ST-segment changes at rest. Among the 60% of the patients who were predicted to have functional capacity of more than 4 METs, only 15% had poor functional capacity at the time of testing. Multivariate analysis for predicting death and new infarction selected only functional capacity (continuous variable in METs), which classified 72% of the patients into a low-risk group with less than a 2% rate of death and new AMI in the first year. The high-risk group (29% of the patients) had an 18% rate of death or new AMI. It is concluded that functional capacity is the most important exercise test variable and that patients likely to have good functional capacity can be identified on the basis of age and ST-segment changes at rest. Further, the level of functional capacity on exercise testing can identify groups of patients with very low and relatively high risk of death or new AMI within 1 year.

(Am J Cardiol 1985;56:839–845)

Exercise testing soon after acute myocardial infarction (AMI) has important prognostic implications.[1] Several exercise test variables, including functional capacity,[2–8] ST-segment depression,[3,9–18] exercise induced-angina pectoris[3,12–14,17,19,20] and ventricular premature complexes[2,5,13,19,21,22] are well established as unvariate prognostic factors. The relation between clinical variables available during the hospitalization and exercise test variables has been evaluated in only a few studies.[5,16,23] If prediction of the exercise test response based on clinical data were possible, then the value of the exercise test would decrease. Prediction of death after AMI has been made with similar accuracy using either clinical data alone, exercise test data alone or a combination of the 2 sets of data.[24]

Patients who undergo exercise testing generally have a low risk of death and new AMI, ranging from 4% to 10% during long-term follow-up.[6,13,15,17,18] Identification

From the Divisions of Cardiology, University of California Medical Center, San Diego; Veterans Administration Hospital; and United States Naval Regional Medical Center, San Diego, California; and the Division of Cardiology, University of British Columbia, Vancouver, Canada. This study was supported by Ischemic Heart Disease SCOR Grant HL 17682 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received December 17, 1984; revised manuscript received May 15, 1985, accepted May 17, 1985.

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TABLE I Differences Between Patients Who Underwent Exercise Testing and Those Who Did Not

	Total	Without Test		With Test		
	n	n	(%)	n	(%)	p Value
No. of pts	1,469	1,003		466		
Men	1,123	741	(74)	382	(82)	0.0008
Age (yr)		64 ± 12		58 ± 12		<0.00001
Previous						
Infarction	433	332	(33)	101	(22)	<0.00001
Heart failure	170	147	(15)	23	(5)	<0.00001
Angina	588	463	(46)	125	(27)	<0.00001
Hospitalization						
Inferior AMI	554	350	(35)	204	(44)	0.001
Subendocardial	318	233	(23)	85	(18)	0.03
Extension	90	73	(7)	17	(4)	0.009
Basal rales	927	667	(67)	260	(56)	0.0001
Bradycardia	642	419	(42)	223	(48)	0.03
VT	382	220	(22)	162	(35)	<0.00001
Maximal heart rate		94 ± 20		92 ± 19		0.01
Minimal systolic BP		103 ± 14		101 ± 14		0.005
Maximal respiratory rate		23 ± 4		22 ± 3		0.0006
Maximal CK		1,092 ± 939		1,393 ± 1,136		<0.00001
Maximal BUN		23 ± 12		20 ± 9		0.0001
Discharge						
Basal rales	103	82	(8)	21	(5)	0.01
Digitalis	544	423	(42)	121	(26)	<0.00001
β-blockers	632	384	(38)	248	(53)	<0.00001
LVEF		0.48 ± 0.14		0.50 ± 0.13		0.01
CT ratio		0.50 ± 0.06		0.48 ± 0.05		<0.00001
Follow-up 1-year	1,223	859	(86)	364	(78)	
Death/new AMI	155	128	(15)	27	(7)	0.0005

The mean ± standard deviation is listed for continuous variables.
AMI = acute myocardial infarction; BP = blood pressure; BUN = blood urea nitrogen; CK = creatine kinase; CT = cardiothoracic; LVEF = left ventricular ejection fraction; VT = ventricular tachycardia.

of subgroups of patients with even lower risk or relatively high risk among patients who undergo exercise testing could have important clinical applications with regard to therapy and follow-up. This study aims to clarify the following questions about the exercise test after AMI: Can an ischemic exercise test response and level of functional capacity be predicted from historical and clinical data available during the hospitalization? Can subgroups of patients who are at very low or relatively high risk of death or new AMI be identified by use of exercise test variables?

Methods

Patients: The study population consisted of 1,469 patients discharged after definite AMI. Among these patients, 466 (32%) underwent treadmill exercise testing around the time of hospital discharge (average discharge day 12 ± 4), but not later than 6 weeks after discharge. The exercise test was performed during the late hospitalization in 80% of the patients and within 2 weeks after discharge in 9%.

The patients were admitted within 24 hours after onset of symptoms to the University of California Medical Center, San Diego (55 patients), San Diego Veterans Administration Hospital (48 patients), U.S. Naval Regional Medical Center in San Diego (197 patients), and Vancouver General Hospital, Vancouver, British Columbia, Canada (166 patients), from January 1, 1979 to November 1, 1984. The data, including exercise test variables, were gathered prospectively on special forms for a data base supported by the Specialized Center of Research (SCOR) on Ischemic Heart Disease at the University of California Medical Center, San Diego. One objective of our SCOR program was to evaluate the prognostic value of various exercise test variables.

The diagnosis of AMI was established by at least 2 of the following criteria: characteristic chest pain; electrocardiographic changes with evolution of Q waves (transmural infarction); and elevated creatine kinase levels. Nontransmural infarction was diagnosed by typical ST-segment and T-wave changes accompanied by elevated creatine kinase levels.

Clinical variables: As previously described in detail,[25] clinical variables included data from the history, physical examination during the hospitalization and at discharge (e.g., maximal heart rate and pulmonary rales), laboratory findings (e.g., enzyme levels), radiographic variables (pulmonary venous congestion and cardiothoracic ratio) and the electrocardiogram (e.g., arrhythmias and ST-segment depression or elevation of at least 0.1 mV at rest). Administration of medications at the time of discharge was also noted.

In a subgroup of 750 patients, of whom 374 also underwent exercise testing, left ventricular ejection fraction (LVEF) was measured either by radionuclide techniques just before discharge or by cardiac catheterization up to 6 weeks after discharge. In another subgroup of 828 patients, of whom 280 underwent exercise testing, the presence of complex ventricular arrhythmias from a 24-hour ambulatory monitoring just before discharge was determined as previously described.[25]

Exercise testing: The exercise test was an optional part of our SCOR study protocol. In general, patients were selected for the exercise test based on the judgment of the attending physician. During the study period, exercise testing early after acute myocardial infarction became more accepted as a safe and useful test. The main reasons for not performing an exercise test were advanced age, poor general condition, severe cardiac dysfunction or disease of other organs precluding adequate exercise.

The 466 patients who underwent exercise testing had a lower frequency of clinical risk factors than patients who did not undergo exercise testing (Table I). Fewer patients who

TABLE II Variables of Univariate Importance for Ischemic Exercise Test Response (Exercise-Induced ST-Segment Depression and Angina)

		Exercise Test Response				
		Normal		Ischemic		
	Total	n	(%)	n	(%)	p Value
No. of pts	374	169	(45)	205	(55)	
Age (yr)		56 ± 13		60 ± 11		0.002
Previous						
Infarction	80	28	(17)	52	(25)	0.05
Angina	95	29	(17)	66	(32)	0.001
Hypertension	146	55	(33)	91	(44)	0.03
Hospitalization						
Peak leukocytes × 10^3	125	92 ± 5		113	78 ± 4	0.007
ST-segment depression	43	11	(7)	32	(16)	0.009
Discharge β blockers	201	79	(47)	122	(60)	0.01

The mean ± standard deviation is listed for continuous variables.

underwent exercise testing had previous heart failure or angina, showed signs of heart failure during the hospitalization or were treated with digitalis. The number of deaths and new infarctions within 1 year was significantly higher among the patients without exercise tests (15%) than in patients with exercise tests (7%).

Exercise test protocol: The exercise test was performed with a standard Bruce protocol[26] in 80 patients (17%), modified Bruce (Sheffield) protocol[27] in 230 (49%) and modified Balke protocol[28] in 36 (8%); in 120 (26%) further modified protocols were selected by the attending physician.

The limiting conditions for the exercise test were angina pectoris in 72 patients (16%), pronounced ST-segment changes (at least 0.2 mV depression or elevation) in 34 (7%), fatigue in 207 (44%), shortness of breath in 81 (17%), claudication in 20 (4%) and severe dysrhythmias in 9 (2%). More than 1 limiting condition was noted in some patients.

If no symptoms developed, the patients continued to exercise in most cases until they approached 75% of maximal age-adjusted heart rate. Tests in 43 patients (9%) without limiting symptoms, where the exercise test was stopped at a low heart rate, were considered indeterminate. Patients taking β-blocking agents were included if a heart rate greater than 100 beats/min was achieved at the termination of exercise, provided a functional capacity above 6 METs (1 MET = 3.5 ml O_2/kg-min) was also attained. These threshold levels were selected empirically in order to exclude patients with low work loads owing to treatment with β-blocking agents.

Medications were continued during the test, with 121 (26%) receiving digitalis, 53 (11%) procainamide and 248 (53%) β-blocking agents. ST-segment changes in patients with bundle branch block or left ventricular hypertrophy, or those receiving digitalis therapy, were considered indeterminate.

Ninety-two patients had indeterminate test results; these results were not analyzed, and 374 patients were left for further study. Among these patients, 295 had been followed for 1 year at the time of this study, of whom 19 died or had new AMIs or both.

Exercise test variables: (1) Cardiac-based reasons for stopping exercise: angina pectoris, pronounced ST-segment changes, or severe dysrhythmias. (2) Presence of typical angina pectoris during the test. (3) Functional capacity in METs, as calculated from the predicted oxgyen consumption in the protocols.[29] Functional capacity was treated both as a continuous variable and a discrete variable with a breakpoint value of 4 METs or less, which was determined to be the best breakpoint for patients who died or had a new AMI, or both, compared with patients without these endpoints. (4) Maximal heart rate at peak exercise work load. (5) Abnormal systolic blood pressure response: decrease or increase of less than 20 mm Hg during maximal exercise. (6) Exercise-induced ST-segment depression: flat or downsloping type of at least 0.1 mV compared with the ECG at rest measured 80 ms after the J point in anterior, lateral or inferior leads. If ST-segment depression at rest was present, further ST-segment depression of at least 0.1 mV was considered as exercise-induced ST-segment depression. (7) Exercise-induced ST-segment elevation: J-point elevation of at least 0.1 mV compared with the ECG at rest, without ST-segment depression in other leads. The ST-segment elevations were required to be in leads other than those exhibiting Q waves. (8) Dysrhythmias: the presence of frequent premature ventricular complexes (more than 6 beats/min), ventricular tachycardia (more than 3 consecutive ventricular complexes) or supraventricular tachycardia (more than 3 consecutive supraventricular premature complexes). (9) Ischemic exercise test response: presence of exercise-induced ST-segment depression as defined above and/or presence of angina pectoris during the test.

Follow-up: Patients were followed up by telephone interview in the year after admission. Information concerning deaths and new AMI was obtained from the death certificate or hospital records in most cases.

Statistics: The Student *t* test was used to compare mean values and a chi-square test to compare incidences of discrete variables between groups. Stepwise linear discriminant function analysis as previously described in detail[30] was performed to evaluate the independent importance of clinical variables for predicting ischemic exercise test responses or a low functional capacity and to evaluate the independent importance of exercise test variables for the prognosis of cardiac death or new AMI within 1 year. The prediction results are based on the jackknife procedure.[31] The results are presented as the percentage of correctly classified patients with the predicted endpoint, percentage of correctly classified patients without an endpoint and the percentage of the total number of patients correctly classified. In addition, the number of patients in the groups predicted either to have or not to have an endpoint was noted and the incidence of endpoints in both groups calculated to give the rates of false-positive and false-negative predictions.

Results

Prediction of ischemic exercise test response: In the 374 patients with exercise tests satisfactory for analysis, only a few clinical variables were related uni-

TABLE III Prediction of Ischemic Exercise Test Response by Discriminant Analysis of Historical Variables and Variables Available During Hospitalization

Variable	Rank	F Value
Previous angina	1	10.1
ST-segment depression at rest	2	7.2
Discharge β-blocking agents	3	6.6
Age	4	7.2
Correct classification	n	%
Ischemic exercise test response	200	58
Normal exercise test response	165	66
Total	365	61
Predicted group with ischemic test	173	47
Ischemic tests in group	116	67
Predicted group with normal test	192	53
Ischemic tests in group	84	44

variately to an ischemic exercise test response, defined as exercise-induced ST-segment depression or angina pectoris or both (Table II). The presence of ST-segment depression on the ECG at rest, indicating evidence of ischemia at rest, was important for predicting an ischemic exercise test response.

LVEF in patients with an ischemic exercise test response (mean 0.50) was not significantly different from that in patients without ischemic exercise responses (mean 0.52). Complex ventricular arrhythmias recorded on 24-hour ambulatory monitoring before discharge was the same in the 2 groups of patients (39%).

When the important variables were included in a discriminant analysis with the occurrence of an ischemic exercise test response as the endpoint, only 4 variables were selected, with the presence of previous angina ranked first (Table III). However, correct classification of patients with and without an ischemic exercise test was 61%, and the rate of false-positive responses (patients with normal tests in the group predicted to have ischemic tests) was 33% and the rate of false-negative responses (patients with ischemic tests in the group predicted to have normal tests) was also high—44%.

Prediction of functional capacity: More clinical variables were important univariately for predicting a low functional capacity (4 METs or less) (Table IV). The presence of ST-segment changes at rest (depression or elevation) was related to a low functional capacity. Also, 66% of patients with poor functional capacity had an ischemic exercise test response, compared to 47% of patients with good functional capacity. As expected, patients with low functional capacity had significantly lower LVEFs. The occurrence of complex ventricular arrhythmias on 24-hour ambulatory monitoring in patients with poor functional capacity (42%) was not significantly different from that in patients with good functional capacity (39%).

In a multivariate discriminant analysis of predictors of poor functional capacity, only age and ST-segment changes at rest were selected (Table V). The overall correct classification of patients with poor functional capacity and with good functional capacity was 68%. A good functional capacity was predicted in 60% of the patients, and among these patients only 15% had a poor test functional capacity.

Exercise test data and prognosis: In the 295 patients followed 1 year with satisfactory exercise tests, among exercise test variables tested univariately, only functional capacity in METs and the occurrence of exercise-induced ST-segment depression were important for death and/or new AMI within 1 year (Table VI).

A discriminant analysis using all exercise test variables selected only the functional capacity in METs (Table VII). Total correct classification was 75%. In the low-risk group of patients (72% of patients, functional capacity greater than 4 METs), fewer than 2% died or had a new AMI within 1 year. In the high-risk group of patients (29% of patients, functional capacity ≤4 METs), 18% reached an endpoint.

Discussion

Selection for exercise testing: Patients selected for exercise testing usually have a more favorable prognosis

TABLE IV Variables of Univariate Importance for Low Functional Capacity (4 METs or Less)

		Functional Capacity				
		>4 METs		≤4 METs		
	Total	n	(%)	n	(%)	p Value
No. of pts	374	274	(73)	100	(27)	
Age (yr)		56 ± 12		64 ± 11		<0.00001
Previous						
Infarction	80	48	(18)	32	(32)	0.004
Angina	95	61	(22)	34	(34)	0.03
Hypertension	146	94	(34)	52	(52)	0.003
Heart failure	14	5	(2)	9	(9)	0.003
Hospitalization						
Maximal heart rate		91 ± 18		96 ± 24		0.02
Maximal BUN		19 ± 7.2		22 ± 9.4		0.002
Anterior AMI	125	83	(30)	42	(42)	0.03
Rest ST-segment changes	138	85	(31)	53	(53)	<0.00001
Discharge						
LVEF		0.52 ± 0.13		0.46 ± 0.13		0.005
CT ratio		0.47 ± 0.05		0.49 ± 0.05		0.003
Procainamide	38	19	(7)	19	(19)	0.001

The mean ± standard deviation is listed for continuous variables.
Abbreviations as in Table I.

than patients who are not subjected to exercise testing.[6,18,24] Among our patients who underwent exercise testing, 7% died or had a new AMI within 1 year, compared with 15% among patients who did not undergo exercise testing.

The patients who underwent exercise testing (32%) were comparable to other populations[5,8,13,15,16] with regard to the incidence of basic clinical characteristics (Table I). However, as in other studies, the occurrence of clinical variables among the patients who underwent exercise testing is influenced by the selection criteria. Among our patients who underwent exercise testing, 56% had basilar rales during the hospitalization, which is in agreement with 48% of the patients showing signs of heart failure in another study.[5] At the time of exercise testing, 26% of our patients were treated with digitalis, compared with previously reported rates of 26%[15] and 48%.[5]

The incidence of death and/or new AMI within 1 year among the patients who underwent exercise testing (7%) was comparable to that in some previous studies (7%,[6] 8%[3]), but lower than that in other studies (10%[5,13,15] and 13%[8]) in which a greater proportion of patients were selected for exercise testing.

Exercise test protocol: The treadmill exercise tests in this study were performed with different protocols as selected by the attending physicians at each hospital. Only 17% were high-level protocols (Bruce), which may overestimate oxygen consumption. Different protocols should not be expected to influence the results, because most of the patients had limiting symptoms. Most other studies have used heart rate–limited tests, but the symptom-limited test is superior for detecting ischemic abnormalities after myocardial infarction.[32] The most frequent reason for stopping exercise was fatigue (in 44%); 16% stopped because of angina, an incidence similar to that reported in previous studies.[6,17]

TABLE V Prediction of Functional Capacity by Discriminant Analysis of Historical Factors and Variables Available During Hospitalization

Variable	Rank	F value
Age	1	41.3
Rest ST-segment change	2	13.9
Correct classification	n	%
Low functional capacity (≤4 METs)	100	66
Normal functional capacity (>4 METs)	274	69
Total	374	68
Predicted group with low capacity	150	40
Patients with low capacity in group	66	44
Predicted group with good capacity	224	60
Patients with low capacity in group	34	15

Ischemic exercise test response: The importance of previous angina pectoris[5] and ST-segment depression at rest[5] for predicting an ischemic exercise test response was confirmed in this study. The occurrence of an ischemic exercise test response could be underestimated, because some patients in this study may not have achieved a sufficient workload to detect ischemia.

In our group of 374 patients who underwent exercise testing and in whom LVEF was measured, we could not confirm the relation between a low LVEF and ischemic test response as previously reported in studies including data from 28[23] and 40[16] patients. The mean LVEF was 0.48 in our patients, compared with 0.44[16] and 0.53[23] in the 2 previous studies. The difference in findings may be explained by small groups of patients in the 2 previous reports.[16,23]

TABLE VI Univariate Relation Between Exercise Test Variables and Death or New Infarction One Year After Admission

		Death/New Infarction			
		Yes		No	
	Total n	n	(%)	n	p Value
No. of pts	295	19	(6)	276	
Cardiac reason for stopping					
Yes	80	7	(9)	73	NS
No	215	12	(6)	203	
Angina during test					
Yes	62	6	(10)	56	NS
No	233	13	(6)	220	
Systolic BP response					
Abnormal	86	7	(8)	79	NS
Normal	206	12	(6)	194	
Dysrhythmias during test					
Yes	25	3	(12)	23	NS
No	270	16	(6)	254	
ST-segment change					
Depression	116	12	(10)	104	0.03
Elevation	31	1	(3)	30	NS
No change	148	6	(4)	142	
Ischemic test response					
Yes	161	14	(9)	147	NS
No	134	5	(4)	129	
METS (mean ±SD)		4.1 ± 1.9		6.2 ± 2.6	0.0001
≤4 (high risk)	84	15	(18)	69	
>4 (low risk)	211	4	(2)	207	<0.00001
Maximal heart rate (mean ± SD)		113 ± 21		121 ± 22	NS

BP = blood pressure; NS = not significant; SD = standard deviation.

TABLE VII Prediction of Death and New Infarction One Year After Admission with Functional Capacity from Discriminant Analysis

Variables	Rank	F Value
METs	1	13.0
Correct classification	n	%
Death/new infarction	19	79
Survival/no new infarction	276	75
Total	295	75
Patients in low-risk group	211	72
Death/new infarction	4	2
Patients in high-risk group	84	29
Death/new infarction	15	18

Multivariate analysis of clinical variables has not been used before with exercise test parameters as endpoints. We found that an ischemic or normal exercise test response cannot be reliably predicted from historical or clinical variables available during the hospitalization.

Functional capacity: The importance of age for predicting functional capacity is not surprising because it is inversely related to age. The mean age of patients with poor functional capacity was significantly higher than that of patients with good functional capacity. In addition, patients with poor functional capacity also had a higher frequency of risk factors and signs of heart failure as previously reported.[5] Therefore, poor functional capacity reflects more advanced heart disease in older patients.

Use of the 2 most important variables selected by multivariate analysis (age and ST-segment changes at rest) indicated that reliable prediction of good functional capacity was possible with only a 15% rate of false-negative results (Table V). We could not predict poor functional capacity because the rate of false-positive responses was 56%. However, prediction of functional capacity overall was more reliable than prediction of an ischemic exercise response.

As an endpoint, functional capacity was dichotomized using a breakpoint value of 4 METs, which corresponded to the best discrimination between patients who did or did not die or have a new AMI. However, the relation between this breakpoint and the clinical status of the patient could be limited because some patients with a functional capacity higher than 4 METs also have clinical signs of heart failure.

Beta-blocking agents: Treatment with β-blocking agents was more frequent among patients who underwent exercise testing compared with those who did not (53% vs 38%). This finding suggests that patients treated with β-blocking agents were younger and in better clinical condition without signs of heart failure at the time of discharge, making them more suitable for exercise testing. Among patients who underwent exercise testing, more with an ischemic exercise test response were treated with β-blocking agents than patients without an ischemic exercise test response (60% vs 47%). This can be explained by a greater frequency of previous angina pectoris in patients with β-blocking drugs (31%) compared with patients not so treated (20%) ($p < 0.02$). If β-blocking agents were more frequently prescribed for patients with angina, it would not be surprising if these patients experienced more angina during testing.

Prognostic exercise test variables: Our results confirm the importance of functional capacity as the most important exercise test variable, as previously reported.[2–8] Survivors without a new AMI within 1 year achieved a significantly higher functional capacity (mean 6.2 vs 4.1 METs). Functional capacity was the only variable selected in multivariate analysis of exercise test variables.

ST-segment depression was univariately important, as reported previously,[3,9–18] but this variable was not selected by the multivariate analysis. Other exercise test variables, particularly functional capacity, are related to ST-segment depression,[6] and when functional capacity is selected first in the multivariate analysis the independent importance of ST-segment depression decreases. The same finding has been confirmed by another recent multivariate study.[8]

The definition of exercise-induced ST-segment depression could influence the prognostic value of this variable. Our definition (flat or downsloping depression of at least 0.1 mV) was in accordance with that in previous studies.[3,5,13–15] We have previously shown that quantitation of the degree of ST-segment depression did not improve its prognostic value.[6]

Prediction of death and new infarction: Use of functional capacity could identify a fairly large low-risk group of patients (72%) with a low rate of death or new AMI (2%) and a smaller group of patients (28%) with a relatively high risk (18%).

Functional capacity in patients subjected to exercise is a good predictor of the outcome 1 year after AMI. The number of prognostic endpoints in this study (19 deaths or new AMIs) precludes further analysis of the high risk group. Additional studies are needed to evaluate whether further prognostic stratification of the high-risk group is possible.

Conclusions: An ischemic exercise test response (ST-segment depression or angina pectoris) cannot be reliably predicted from historical or clinical variables from the hospitalization. Patients likely to have good functional capacity can be identified by using age and ST-segment changes at rest. Good functional capacity is the most important exercise test variable for identifying a low-risk group with very low risk of death and new AMI within 1 year. A group of patients at relatively high risk can be identified by a poor exercise test functional capacity.

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Repeated Quantitative Angiograms in Coronary Arterial Aneurysm in Kawasaki Disease

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Accurate evaluation of the extent of coronary artery lesions complicating Kawasaki disease is clinically important in patient management. Based on a total of 188 coronary angiograms and retrospective follow-up observations, the condition of coronary aneurysms was quantitatively graded as: 0 (normal)—no significant enlargement in any portion of the coronary artery; I (mild)—aneurysmal dilatation of the coronary artery evident but localized, with a maximal diameter of less than 4.0 mm; II (moderate)—maximal diameter of coronary aneurysms between 4.0 and 8.0 mm, regardless of body size; III (severe)—giant aneurysms, with the maximal diameter greater than 8.0 mm. Most mild coronary aneurysms regressed to normal within a short time, and the patient's prognosis was good. The course of grade II aneurysms varied, depending on initial angiographic coronary diameter, but all were eventually reduced in coronary size. In contrast, grade III aneurysms usually progressed to become obstructive or stenotic coronary lesions, or the large aneurysm persisted. Follow-up observations revealed that the course of coronary artery disease depended on the size and distribution of aneurysms at initial angiography. This grading of the severity of coronary lesions may provide useful criteria for predicting the prognosis of patients with Kawasaki disease. (Am J Cardiol 1985;56:846–851)

Kawasaki disease, an acute febrile illness that affects predominantly infants and young children,[1] produces coronary aneurysms during the acute stage of the illness.[2] Sudden death may result from myocardial infarction owing to thrombotic occlusion of the coronary artery.[3,4] More than half of the coronary aneurysms can regress within 1 year after onset, but some may progress into completely obstructive or markedly stenotic coronary lesions.[5] Because the morbidity and mortality of Kawasaki disease mostly depends on the extent of associated coronary artery disease, it is particularly important to assess accurately the condition of coronary lesions and to observe carefully their natural course. In the present study, we classified the severity of coronary aneurysms caused by Kawasaki disease based on quantitative coronary cineangiograms and on the retrospective study of follow-up observations. According to this classification, the outcome of coronary artery disease and factors that affect the natural course were also studied.

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Methods

Patients: The present study consists of 138 patients with Kawasaki disease who underwent coronary angiography between January 1980 and December 1984 for the evaluation of coronary artery involvement. There were 80 boys and 58 girls, aged 3 months to 12 years (mean 2 years, 10 months) at the time of angiography. The interval from angiographic examination and disease onset ranged from 24 days to 9 years, and 106 patients (76.8%) underwent initial angiography within 3 months of onset. Sixty patients were found to have no cardiovascular complications at the first angiographic study, and of the remainder, 50 patients, including 38 with right and 48 with left coronary lesions, underwent repeat angiography for follow-up evaluation between 3 and 22 months (mean 11) after the initial study. Thus, 188 angiographic studies were evaluated in the current investigation. All patients who underwent repeat angiography had been receiving an antiplatelet agent, ticlopidine, 5.0 mg/kg per day, since the convalescent stage of the illness.

Protocol: The patients gave informed consent after the procedure was explained. Each patient underwent right and left coronary cineangiography in the anteroposterior projection at 60 frames/s after 0.3 to 0.5 ml/kg of metrizamide was hand injected into each coronary artery. The projected image of the end-diastolic frame was accurately traced, and thereby coronary artery size was measured. In patients without coronary lesions, the diameter was measured at the proximal segment of the right coronary artery close to the aorta and at the midportion of the left main coronary artery. When associated coronary aneurysms were present, the maximal diam-

eter of those perpendicular to the axis of the coronary artery was measured in the individual vessel. In addition to the measurement of coronary diameter, particular attention was paid to the progression into obstructive coronary changes in the repeat angiographic evaluation.

Coronary artery aneurysms were angiographically classified as solitary, multiple or extensive, according to the distribution and extent of lesions. The morphologic feature of aneurysms was classified into saccular, sacculofusiform or fusiform shape, based on the ratio of short and long axes of aneurysmal lesions.[6] The predominant lesion was distinguished as located in the proximal, middle or distal portion of the right coronary artery, and the left main, anterior descending or circumflex of the left coronary artery. The dominant coronary type was determined according to the criteria of the Coronary Artery Surgery Study.

Results

Normal coronary artery size in infants and children: Sixty patients had no associated coronary aneurysms, not even transient dilatation of the coronary artery during the acute stage of the illness. Coronary artery diameters of these subjects served as the normal control values (Fig. 1). A significant correlation was found between body surface area (BSA) and coronary artery size ($r = 0.81$ in the right coronary artery, $r = 0.74$ in the left coronary artery). In the right coronary artery, all measurements of the normal diameter were 2.5 mm or less in the patients with a BSA of less than 0.5 m^2. These values were 3.0 mm or less in the patients with BSA between 0.5 and 1.0 m^2, but were 3.0 mm or more with BSA of more than 1.0 m^2. Similar values were measured in the left coronary artery in all but 1 patient, with a BSA of 0.99 m^2 and a coronary diameter of 3.2 mm.

Coronary artery size and the extent and distribution of coronary artery involvement: The relation between the maximal diameter and the extent and distribution of coronary lesions was examined in 38 and 48 patients associated initially with right or left coronary aneurysms, respectively. The maximal diameter of a coronary aneurysm in the solitary lesion was usually 4.0 mm or less in both coronary arteries, whereas multiple or extensive lesions were usually 4.0 mm or more regardless of BSA (Fig. 2). As a result, these lesions

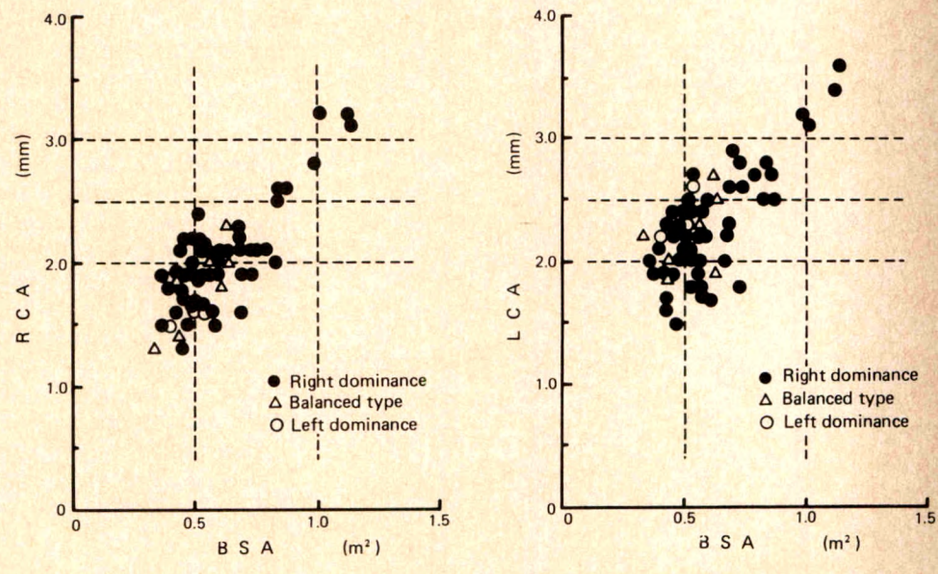

FIGURE 1. Relation between normal coronary artery diameter and body surface area (BSA). LCA = left coronary artery; RCA = right coronary artery.

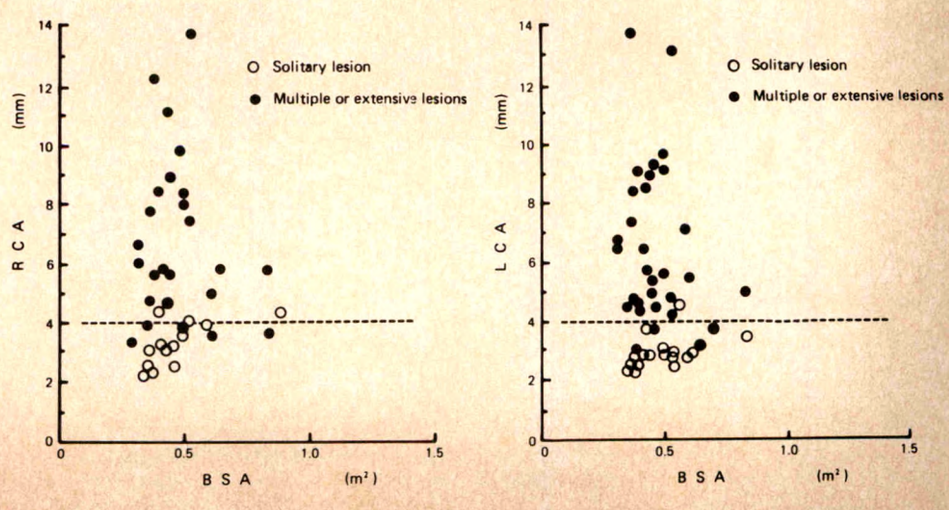

FIGURE 2. Relation between maximal diameter of coronary aneurysms and body surface area (BSA). LCA = left coronary artery; RCA = right coronary artery.

could be arbitrarily separated into groups at 4.0 mm coronary artery diameter, despite a slight overlap between the 2 groups.

Changes in coronary artery size: Coronary aneurysms of initial diameter over 4.0 mm were recognized in the right coronary artery in 25 patients and in the left coronary artery in 28 patients. Changes in size at follow-up, with or without alterations into obstructive coronary lesions, are indicated in Figures 3 and 4. In the right coronary artery, 8 patients with initial coronary aneurysms 8.4 mm or larger were proved to have obstructive coronary lesions at follow-up angiography, except for 2 patients, in whom giant aneurysms persisted almost without changes in coronary size. In contrast, all coronary aneurysms initially 7.8 mm or smaller were markedly smaller and none of the patients in this group showed obstructive coronary artery alterations at the repeat angiographic study.

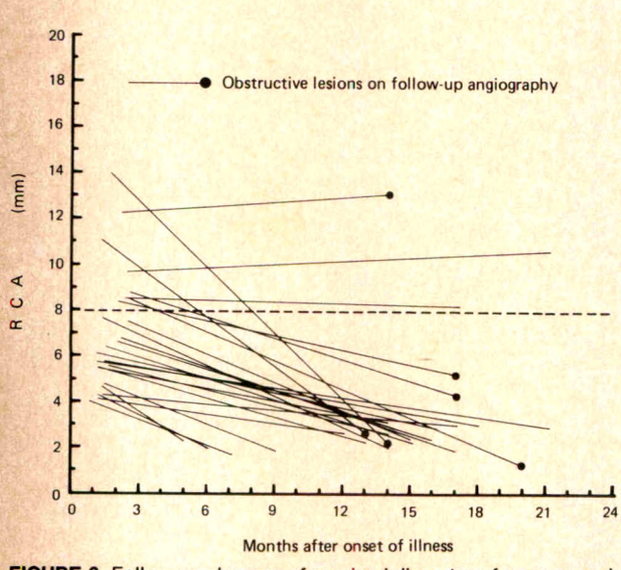

FIGURE 3. Follow-up changes of maximal diameter of aneurysms in the right coronary artery (RCA).

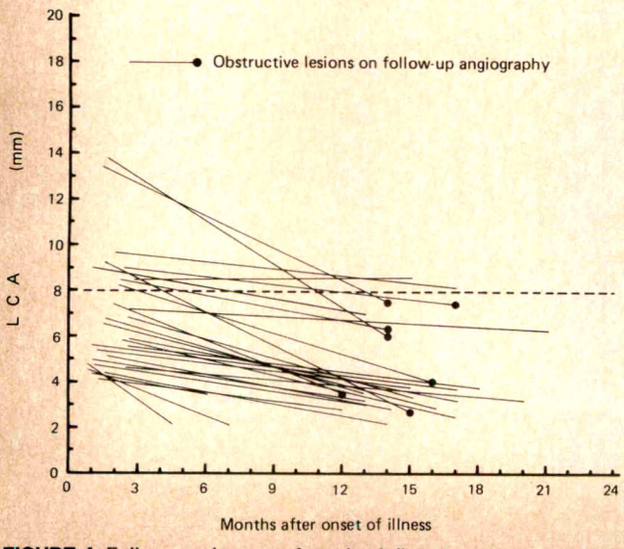

FIGURE 4. Follow-up changes of maximal diameter of aneurysms in the left coronary artery (LCA).

At the follow-up study of left coronary lesions, of 11 patients with initial aneurysms 7.2 mm or larger, coronary aneurysms changed into obstructive lesions in 7 patients and the coronary size was not significantly altered in 4. In all patients with left coronary aneurysms 6.8 mm or smaller, coronary artery diameter was substantially reduced. From these results, we set a common separation point of 8.0 mm in diameter to predict the prognosis of both right and left coronary lesions.

Classification of severity of coronary artery aneurysm: Based on the present results, the severity of coronary artery lesions caused by Kawasaki disease were graded as follows: *Grade 0* (normal)—no significant enlargement in any portion of the coronary artery. Usually the maximal diameter of the coronary artery is less than 2.5 mm in patients with a BSA of less than 0.5 m^2 and less than 3.0 mm in those of BSA between 0.5 and 1.0 m^2. *Grade I* (mild)—apparent aneurysmal dilatation of the coronary artery is evident, but localized with a diameter of less than 4.0 mm. Coronary aneurysms of mild degree are most frequently seen at the proximal segment of the right coronary artery and at the bifurcation of the left anterior descending and left circumflex coronary artery, indicating a "web" appearance (Fig. 5). *Grade II* (moderate)—the maximal diameter of coronary aneurysms between 4.0 and 8.0 mm, regardless of age and BSA. Coronary artery lesions in this group may be solitary, multiple or extensive (Fig. 6). If coronary lesions are multiple or extensive even with a maximal coronary size of less than 4.0 mm, the lesion should be classified as grade II. *Grade III* (severe)—giant aneurysms of the coronary artery with a maximal diameter greater than 8.0 mm. Generally, coronary lesions are extensive and diffuse, involving more than 1 vessel (Fig. 7).

Follow-up evaluation of coronary artery lesions: The changing outcome of right or left coronary artery lesions found shortly after the acute stage of Kawasaki disease was observed in 50 patients undergoing initial angiography within 3 months after onset of the disease (Fig. 8). Follow-up angiography was performed in selected patients when coronary aneurysms were proved

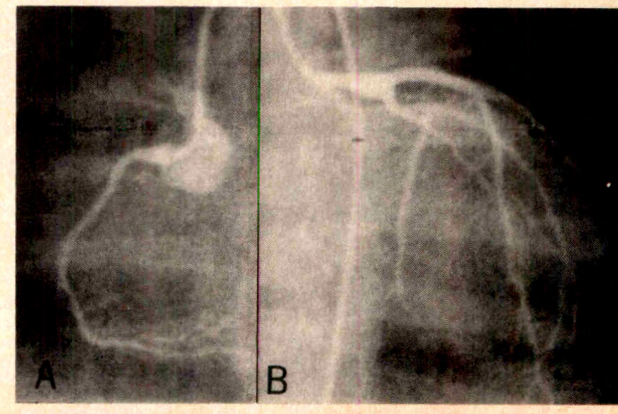

FIGURE 5. Right (**A**) and left (**B**) coronary aneurysms of mild degree (grade I) documented on coronary angiograms. Mild aneurysms are most frequently seen at the bifurcation of the left anterior descending and the left circumflex coronary arteries, giving a "web" appearance.

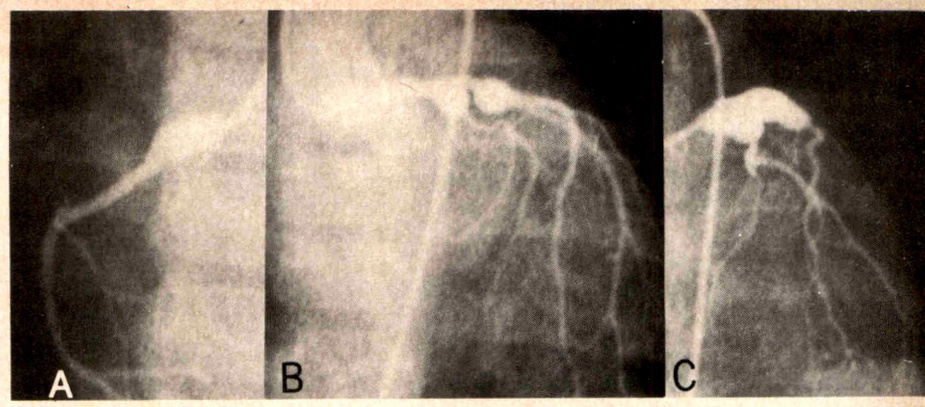

FIGURE 6. Coronary aneurysms of moderate degree (grade II) show various distributions: solitary (**A**), multiple (**B**) or extensive (**C**).

to have regressed to normal appearance on serial 2-dimensional echocardiography, and was performed about 1 year after initial angiography in the remaining patients. In both coronary arteries, most initial coronary lesions of grades I and II regressed to normal or improved to grade I at follow-up study, whereas almost all grade III lesions progressed to become obstructive lesions (Fig. 9) or were unchanged.

Factors influencing the course of coronary artery lesions: To investigate factors that influence the natural course of coronary artery disease, the subjects (38 with right and 48 with left coronary lesions) were separated into 2 groups. Group I included patients whose aneurysms became smaller or regressed to normal at follow-up angiography; group II included patients whose aneurysms progressed into obstructive lesions or did not change. The effects of the following factors on the outcome of coronary lesions in each group were examined: patient's age at onset of Kawasaki disease; gender; dominant coronary type; whether pulse corticosteroid therapy was performed during the acute febrile period; and the characteristics of coronary aneurysms documented at initial angiography, such as the grade of severity described herein, location, distribution and morphologic characteristics. The number of subjects in each item is listed in Table I and statistical analysis by chi-square test revealed that the grade represented by the condition of the coronary artery and the distribution of lesions in both coronary arteries were significantly related to the differences between the 2

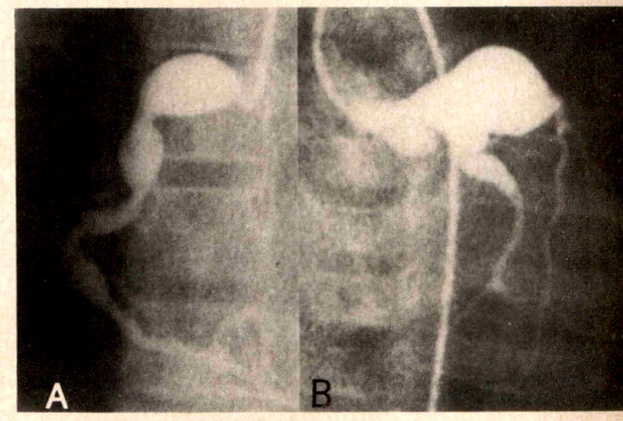

FIGURE 7. Right (**A**) and left (**B**) coronary aneurysms of severe degree (grade III) documented on angiography.

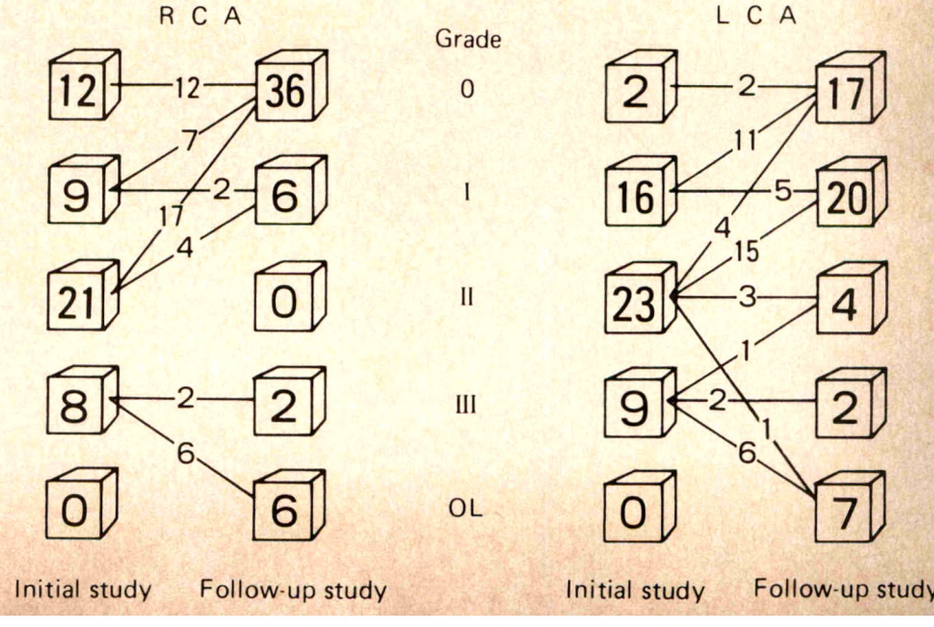

FIGURE 8. Follow-up evaluation of coronary artery lesions. LCA = left coronary artery; OL = obstructive lesions; RCA = right coronary artery.

TABLE I Factors Influencing the Natural Course of Coronary Artery Aneurysm After Kawasaki Disease

	RCA		LCA	
	Group I (n = 30)	Group II (n = 8)	Group I (n = 35)	Group II (n = 13)
Age (mo) (mean ± SD)	24 ± 26	26 ± 23	21 ± 20	21 ± 20
Sex				
Male	16	6	21	11
Female	14	2	14	2
Dominant coronary type				
Right	27	5	27	8
Balanced	2	2	6	2
Left	1	1	2	3
Glucocorticoid therapy	11	2	13	5
Grade of coronary aneurysm				
I	9	0 †	16	0 †
II	21	0 †	19	3 †
III	0	8 †	0	10 †
Location of coronary aneurysm				
Right coronary artery				
Proximal	19	5		
Mid	7	3		
Distal	4	0		
Left coronary artery				
Left main			23	5
Left anterior descending			10	6
Left circumflex			2	2
Distribution of coronary aneurysm				
Solitary	12	0 *	11	0 *
Multiple	16	3 *	8	4 *
Extensive	2	5 *	16	9 *
Morphology of coronary aneurysm				
Saccular	2	0	1	0
Sacculofusiform	19	5	16	11
Fusiform	9	3	18	2

* $p < 0.05$. † $p < 0.01$ between the groups.
Group I consists of subjects whose coronary lesions improved on follow-up angiography; group II consists of subjects whose coronary lesions became worse.
SD = standard deviation.

groups. Factors other than the size and distribution of the coronary artery were shown not to contribute to the natural course of coronary artery disease.

Discussion

Coronary artery aneurysm is a serious cardiovascular complication of Kawasaki disease, which occurs in 15 to 20% of patients with the illness.[7,8] The size and distribution of coronary lesions have a broad spectrum, from transient, slight enlargement to giant aneurysms. Two-dimensional echocardiography has been used to evaluate the extent of these coronary artery lesions.[8–10] However, echocardiographic measurements of coronary artery size have some limitations,[11] with unsatisfactory results in the detection of slight coronary changes as well as obstructive and stenotic coronary lesions. Angiographic evaluation, therefore, may be required for accurate and objective assessment of coronary artery involvement of this disease.

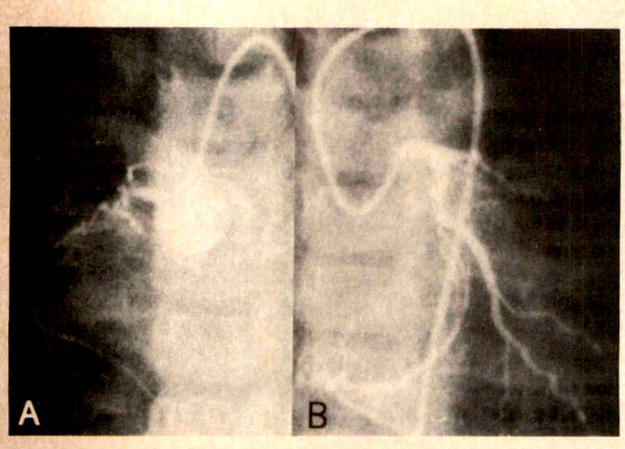

FIGURE 9. Obstructive lesions documented on coronary angiography. **A,** segmental stenotic lesions of the right coronary artery suggesting coronary recanalization. **B,** complete obstruction of the left anterior descending coronary artery.

Angiographic measurements of the normal coronary diameter in infants and children varied depending on body size and the dominant type of the coronary artery.[10] Based on the present results, we could define the upper limit of normal value for coronary artery diameter in terms of BSA. Although somewhat higher values for left coronary diameter and lower values for right coronary diameter were recognized in patients with left dominance of the coronary artery, the normal range described herein was considered applicable to almost all patients regardless of the dominant coronary type.

A close relation was found in both coronary arteries between maximal size and distribution of coronary lesions, and we can separate into 2 groups, grade I and II, as to the severity of coronary lesions at the critical size of 4.0 mm in diameter. Giant aneurysms, of the maximal

diameter of more than 8.0 mm, were associated with a serious prognosis with respect to coronary lesions. Despite administration of antiplatelet drugs, large aneurysms resulted more readily in thrombotic occlusion of the coronary artery, or even if thrombus formation was averted, these large aneurysms remained almost unchanged irreversibly. In contrast, coronary lesions of less than 8.0 mm tended to regress over time. As a result, the coronary artery size of 8.0 mm may represent the critical level to distinguish whether reversible changes of regression may develop in the course of the disease. From all the results, including follow-up observations, we have classified from grade 0 to grade III the severity of coronary artery aneurysms after Kawasaki disease, taking into consideration the size and prognosis of the coronary lesions.

The effect of treatment during follow-up may contribute to the changing outcome of coronary artery lesions. Kato et al[5,7] suggested that aspirin reduced the incidence of coronary artery thrombosis, but their observations in conjunction with the extent of coronary lesions remained obscure. In the present study an antiplatelet agent was uniformly given to all patients after the acute period of the illness, and thus the effect of treatment was unrelated. On the other hand, corticosteroid[7,12] may increase blood coagulability and has the risk of delaying the healing process of coronary arteritis, resulting in the occurrence of coronary aneurysms. However, our study indicates that this agent did not play a significant role in the natural course of coronary aneurysms already developed.

The current study also indicates that the outcome of coronary artery disease was affected only by the size and distribution of the initial coronary lesions. Morphologic characteristics and location of initial coronary aneurysms and coronary dominant type appeared not to be directly related to alterations in the lesions. The major determinant of the prognosis was the initial size of the coronary aneurysms, and therefore we can predict the course of coronary artery disease from angiographic findings shortly after onset of the illness.

Mild coronary aneurysms may return to normal within a short time. The course of moderate-sized aneurysms (grade II) varies, depending on initial size and distribution, eventually with marked reductions in coronary size in most instances. From the clinical viewpoint, the prognosis of patients with grade II aneurysms appears not to be serious, but premature atherosclerotic changes of the coronary artery should be followed carefully.[13] Giant coronary aneurysms (grade III) as well as obstructive coronary lesions were usually associated with impaired left ventricular function resulting from myocardial ischemia.[14] Furthermore, myocardial infarction exclusively occurs in association with large aneurysms or obstructive lesions following Kawasaki disease.[3,14,15] Of clinical importance is the prevention of coronary artery disease, and even if coronary aneurysms should occur, every effort should be made to preclude the development of very large aneurysms.

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Identification of Best Electrocardiographic Leads for Diagnosing Myocardial Infarction by Statistical Analysis of Body Surface Potential Maps

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This study describes a practical approach for the extraction of diagnostic information from body surface potential maps. Body surface potential map data from 361 subjects were used to identify optimal subsets of leads and features to distinguish 184 normal subjects from 177 patients with myocardial infarction (MI). Multivariate analysis was performed on 120-lead data, using as features instantaneous voltage measurements on time-normalized QRS and STT waveforms. Several areas on the map, most of which were located outside the precordial region, contained leads with important discriminant features; 2 of the 3 limb leads (aVR and aVF) also exhibited high diagnostic capability. A total of 6 features (mostly STT measurements) from 3 locations accounted for a specificity of 95% and a sensitivity of 95%; these were the right subclavicular area, the left posterior axillary region and the left leg. As a comparison, the same number of features from the standard 12-lead electrocardiogram yielded a sensitivity of 88% for a specificity of 95%. To investigate the repeatability of the results, the entire population was separated into a training set (100 normal subjects and 100 patients with MI) and a testing set (84 normal subjects and 77 patients with MI); computing a discriminant function on the training set and applying it to the testing set only moderately deteriorated the diagnostic classification. It is concluded that this approach achieves efficient information extraction from body surface potential maps for improved diagnostic classification. (Am J Cardiol 1985;56:852–856)

Data reduction and information extraction are now the fundamental problems in the analysis of electrocardiographic body surface potential maps. Extensive arrays of electrocardiograms are being used to obtain high-quality surface maps; however, in some important applications, such as exercise testing and coronary care unit recordings of patients with acute myocardial infarction (MI), the smallest subset of leads that still contains the essential information present in the complete map may be desirable. Various subset studies have sought the subset that would provide optimal signal representation.[1–3] However, the subset of leads that optimally accounts for the signal information in body surface potential maps is not necessarily optimal for diagnostic classification. To identify the best combinations of electrocardiographic leads and their features for optimally representing diagnostic information characteristic of MI, we performed multivariate analysis of map data, consisting of 120 simultaneously recorded leads, from 184 normal persons and 177 patients with MI.

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Methods

Study population: Three hundred sixty-one subjects were studied. Group A consisted of 184 normal control subjects; group B consisted of 177 patients who had had MI. Group A subjects had no evidence of heart disease by history, physical examination, 12-lead electrocardiogram and echocardiogram. They ranged in age from 20 to 50 years (mean 34). Group B patients had a typical history of cardiac chest pain and characteristic changes in enzyme levels, and in most cases the diagnosis of MI was substantiated by coronary angiography and ventriculography; this group consisted of 44 women and 133 men and included 39 patients with acute MI (less than 1 week), 30 patients with recent MI (between 1 week and 1 month) and 108 patients with old MI (more than 1 month). Patients in this group were 34 to 71 years old (mean 55). All patients with MI were grouped together because breakdown of the population according to the location of the infarct would have yielded subgroups far too small for reliable statistical analysis.

Body surface potential mapping: For each subject, we recorded simultaneously on digital tape the electrocardiographic signals from 117 torso and 3 limb electrode sites, sampling each channel 500 times per second and using the Wilson central terminal as a reference potential. The tracing quality was monitored visually during the recording. Later, the stored data were processed by performing selective averaging, and again carefully inspected and edited. Details of the

procedure have been reported.[4] We time-normalized separately the QRS waveform and ST-T waveform and represented them by 70 and 180 points, respectively.

We computed averaged 120-lead maps separately for the normal and the MI populations by averaging sample-by-sample time-normalized electrocardiograms from subjects in each group. Difference maps were then calculated by subtracting corresponding sample values of 120 averaged signals of the normal and MI groups. Although difference maps could be viewed as a means for guiding the selection of optimal leads and features for the separation of the 2 groups, they do not truly reflect the ability of measurements to discriminate, because they fail to take into account the intragroup variability. Therefore, a particular kind of difference map was designed, aiming at representing the discriminant power of each sampling point of each of 120 signals. The discriminant maps were obtained by dividing each instantaneous difference with the corresponding standard deviation computed from the pooled population. The values thus achieved, referred to as discriminant indexes, were in fact strictly proportional to corresponding Student t-test statistics and provided information on the capability for each measurement, in each lead, to separate the MI group from the normal group. Although inspecting discriminant maps may provide clues for selecting the best leads and for extracting optimal features for any bigroup or multigroup differentiation, we attempted to verify this by more rigorous statistical analysis.

Feature extraction and statistical analysis: We used instantaneous amplitude measurements obtained by sampling time-normalized QRS and ST-T waveforms at equal intervals; this resulted in 8 samples for QRS and 7 samples for STT, i.e., 15 × 120 per subject. The statistical procedure involved 2 steps that were performed by programs from the Biomedical Computer Program library (BMDP 7M).[5] First, the best classifiers were selected from the total number of available features by a stepwise selection; then these selected classifiers were combined into the properly weighted linear discriminant functions.

Because the number of variables was so large (1,800 instantaneous measurements per patient), the program processed 80 input variables at a time and selected the 20 best from each batch, repeating the procedure until it obtained a final set of 20 optimal classifiers. Varying the composition of the batches and their order of entry did not affect the first 8 classifiers selected.

Results

The 120-lead discriminant map for normal subjects and patients with MI (Fig. 1) reveals that: (1) Leads with the largest discriminant indexes (e.g., leads located

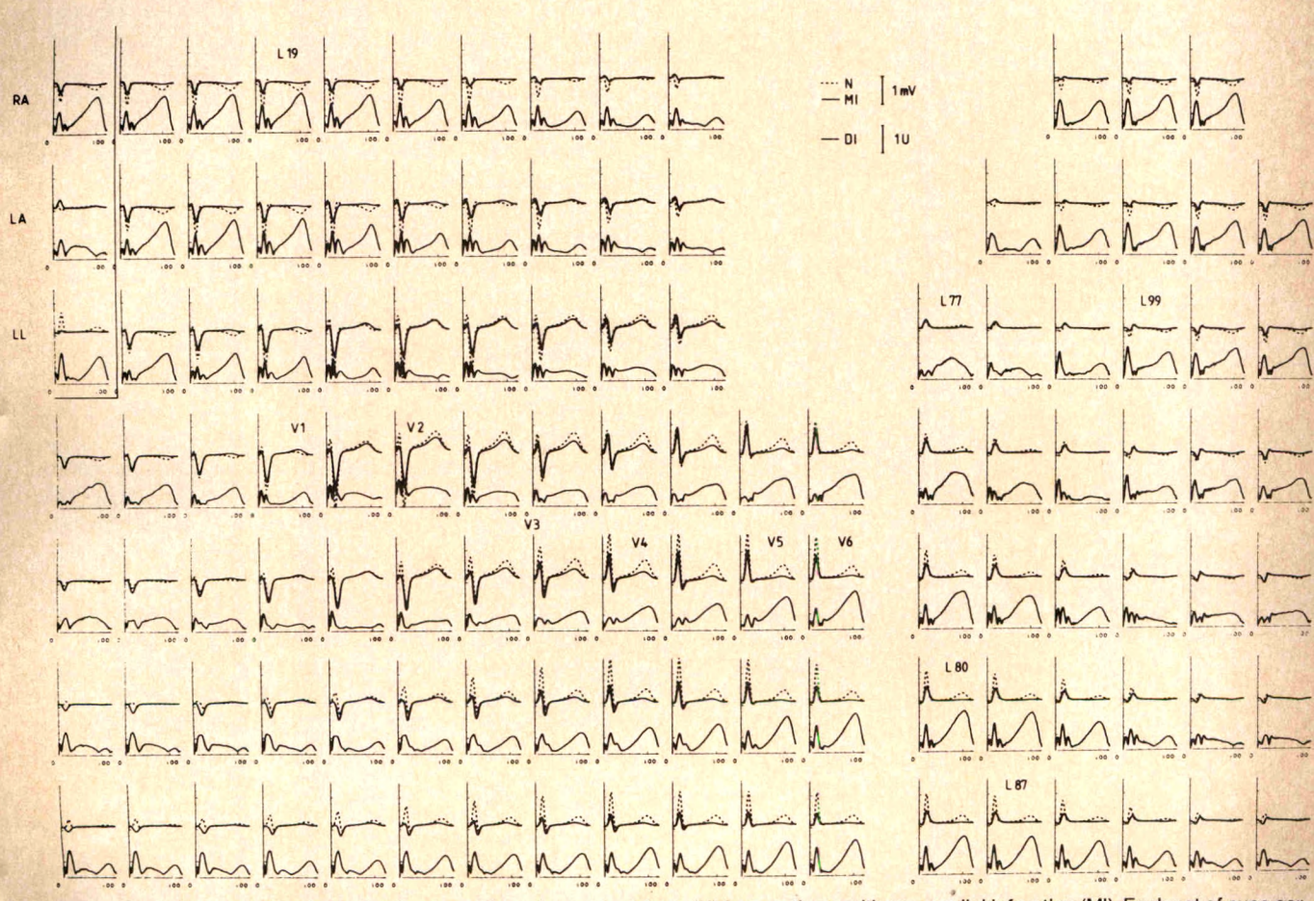

FIGURE 1. Discriminant 120-lead map for the separation of normal subjects (N) from patients with myocardial infarction (MI). Each set of axes corresponds to electrode sites; the **larger box** in the **upper left** corner contains the 3 unipolar limb leads: right arm (RA), left arm (LA), left leg (LL). The **top row** is at the level of the sternal notch and the **bottom row** at the ombilical level. A wider vertical gap separates the anterior from the posterior portion of the thorax. Electrode sites are labeled: V_1 to V_6 for the precordial leads and L 19, L 77, L 80 and L 99 (see text). Each axis set contains 3 curves: the 2 superimposed upper tracings represent averaged, time-normalized (every second point is plotted) electrocardiographic waveforms for normal subjects (**dotted line**) and patients with MI (**solid line**), respectively; the **bottom curve** depicts the absolute value of the instantaneous discriminant index as it varies in time. The amplitude of the discriminant index (DI) equals 1 unit (1U) when the corresponding mean voltages for normal subjects and patients with MI are 1 (pooled) standard deviation apart.

TABLE I Differentiation Between 184 Normal Subjects and 177 Patients with Myocardial Infarction Using Measurements on 120-Lead Data*

Stepwise Selection of Variable Type	Specificity (%)	Sensitivity (%)	Performance† (%)
Lead 80 6/8 ST-T	89	88	88
LL or aVF 4/8 QRS	89	90	90
Lead 19 3/8 ST-T	92	92	92
Lead 77 4/8 ST-T	93	94	93
Lead 99 2/8 QRS	94	94	94
Lead 19 6/8 ST-T	95	96	96

* Instantaneous measurements (8 QRS and 7 ST-T variables).
† ½ (specificity + sensitivity).

in the right subclavicular, the lower left anterior/posterior axillary areas and the upper dorsal region) tend to form clusters of 3 or more similar waveforms; isolated leads such as right arm and left leg also exhibit high discriminant index values. (2) The overall discriminant ability of the T wave is higher than that of the QRS

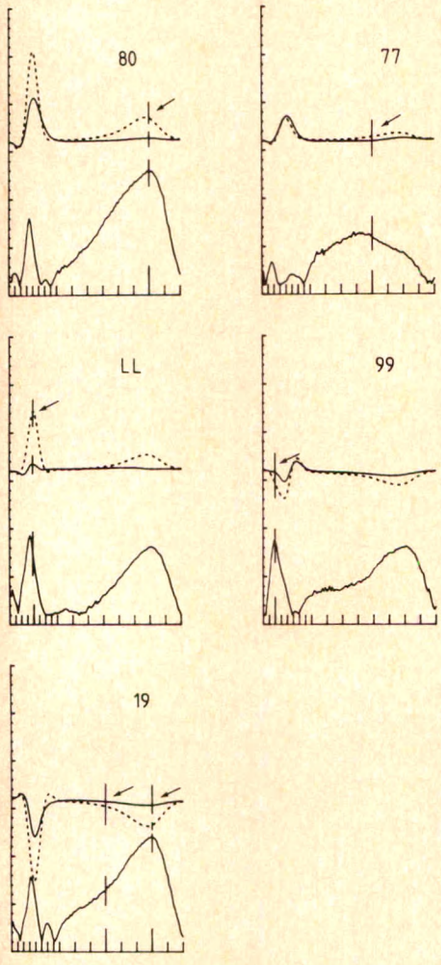

FIGURE 2. The 6 best measurements of the linear discriminant function computed for the separation of the normal group from the myocardial infarction group are shown. This figure shows leads 80, LL, 19 and 99 (same as Figure 1) from which the optimal discriminant features (Table I) are extracted. Signals from normal subjects (**dotted line**) and patients with myocardial infarction (**solid line**) are averaged, time-normalized and superimposed. The **bottom curve** depicts the absolute value of the discriminant index as it varies in time (see text); the marks on the **abscissa** represent the 8 equidistant time instants. **Arrows** point to that part of the signal selected in the stepwise discriminant procedure.

TABLE II Repeatability of the Diagnostic Results*

	Specificity (%)	Sensitivity (%)	Performance† (%)
Training set (100 N and 100 MI)	96	95	96
Testing set (87 N and 77 MI)	93	94	93

* Six instantaneous measurements (listed in Table I) are used.
† ½ (specificity + sensitivity).
MI = patients with myocardial infarction; N = normal subjects.

complex; in most leads the discriminant ability is restricted exclusively to QRS or STT; the "best" leads, however (e.g., leads 19 and 80), perform well in both intervals. (3) The maximal discriminant index during depolarization often coincides with the peak of QRS, which is between the 3/8 and the 4/8 QRS (e.g., left leg and lead 19), but it can also appear early in QRS as in lead 99. (4) Except for leads V_5 and V_6, the precordial leads have lower discriminatory capacity than do the limb leads.

Table I is a list of the results of the discriminant analysis. Only the first 6 variables are tabulated, because little improvement was noted beyond this point. The bulk of the separation (92% correctly classified patients) is achieved with the first 3 variables, measured on leads 80, aVF and 19, respectively. These 3 leads originate from the sites previously described as containing maximal diagnostic capability. The discriminant index for lead 77 peaks in late ST and early T, a pattern different from those in the other leads with high discriminant T indexes. Similarly, the maximal discriminant index is for lead 99 in early QRS. These discrepancies suggest the presence of independent information in these leads. The first 6 measurements selected by the stepwise procedure are shown in Figure 2 and listed in Table I.

To investigate the repeatability of the diagnostic results, we separated the available population into a training set (100 normal subjects and 100 patients with MI) and a testing set (84 normal subjects and 77 patients with MI). A new linear discriminant function was computed in order to separate the 2 groups of the training set. Running the thus calculated discriminant function on the testing set permitted the classification of the remaining patients. The results of this investigation are shown in Table II. A moderate overall deterioration of about 2% was noted.

The diagnostic performance achieved with multivariate analysis on body surface potential maps was also compared with the standard 12-lead electrocardiogram. The first 3 features, accounting for a sensitivity of 84% (specificity kept at 95%), originated from leads aVR (STT), aVF (QRS) and V_6 (STT). Also, the stepwise procedure was repeated by restricting the choice of leads to the 3 best leads previously selected (leads 80, aVF and 19). The results are shown in Table III. The difference of performance between the 2 lead sets was statistically very significant ($p < 0.001$).

Table IV shows the discrepancy between optimal signal representation and optimal diagnostic representation for lead subsets. In a separate study using the same data, we designed a stepwise procedure for se-

TABLE III Diagnostic Performances of 120-Lead Body Surface Potential Maps: Comparison with Selected Lead Systems*

	SE (%)	Missed Cases
120-lead BSPM	96	16
Standard 12-lead ECG	88	31
3 "best" leads	95	18

* Specificity is kept at 95%.
Six instantaneous measurements are used as variables.
BSPM = body surface potential maps; ECG = electrocardiogram; SE = sensitivity.

TABLE IV Signal Information Versus Diagnostic Information

	Best Three Leads in Terms of Signal Prediction (Leads 21, 45, 56)	Best Three Leads in Terms of Diagnostic Separation (Leads 19, 80, aVF)
A. Reconstruction of 120-Lead Maps from Three Leads		
Mean RMS voltage map (μV)	216.1	216.1
Mean RMS residue (μV)	25.3	40.0
Mean RMS error (%)	11.7	18.5
Mean RMS resynthesis (%)	88.3	81.5

B. Diagnostic Classification of 184 Normal Subjects and 177 Patients with Myocardial Infarction

SP (%)	SE (%)	SP (%)	SE (%)
95	82	95	95

MI = myocardial infarction; N = normal; RMS = root-mean-square; SE = sensitivity; SP = specificity.

lecting leads that optimally predicted all the remaining ones in a least-squares, best-fit sense. After 3 steps, the total signal information accounted for reached 88.3% of the root-mean-square voltage. The selected leads were located in high-voltage areas (Fig. 3). With specificity kept at 95%, the diagnostic leads had 95% sensitivity even though they represented only 81.5% of the signal information.

Discussion

Limitations of the study: This study's main limitation is its restriction to a comparison between 2 rather clear-cut groups. Therefore, the optimal diagnostic leads arrived at are only valid for these groups. Before they can be said to have more general diagnostic use, they must be tested in new independent samples. Although other pathologic groups will probably require different lead sets, each of these sets may find its particular clinical application, such as in the coronary care unit or in the exercise electrocardiography laboratory.[6,7]

Discriminant power of body surface potential maps: The differences between averaged normal and MI maps do not necessarily indicate which leads and measurements can be considered potential discriminators. In fact, the largest absolute differences are observed near the vertical level of lead V_4 for QRS and between leads V_4 and V_5 for ST-T, but inspection of the discriminant map (Fig. 1) shows that neither area displays maximal diagnostic capabilities during QRS or ST-T. We therefore turned to discriminant maps in which each difference was scaled by the pooled standard deviation; this yielded instantaneous values (discriminant indexes), which were plotted as a function of time. Peripheral areas of the maps (including the limb leads) with the smallest unscaled differences have the largest scaled differences; this situation is reversed in the precordial leads, in which the large differences are offset by the equally large interindividual variability. Although most of the best leads (leads 19, 80 and aVF) that were found by statistical analysis were identified from the discriminant map, "good" areas (e.g., the lower anterior thoracic row at the umbilical level for QRS and the high dorsal region below the neckline for ST-T) did not contribute to the final subset, and other, seemingly

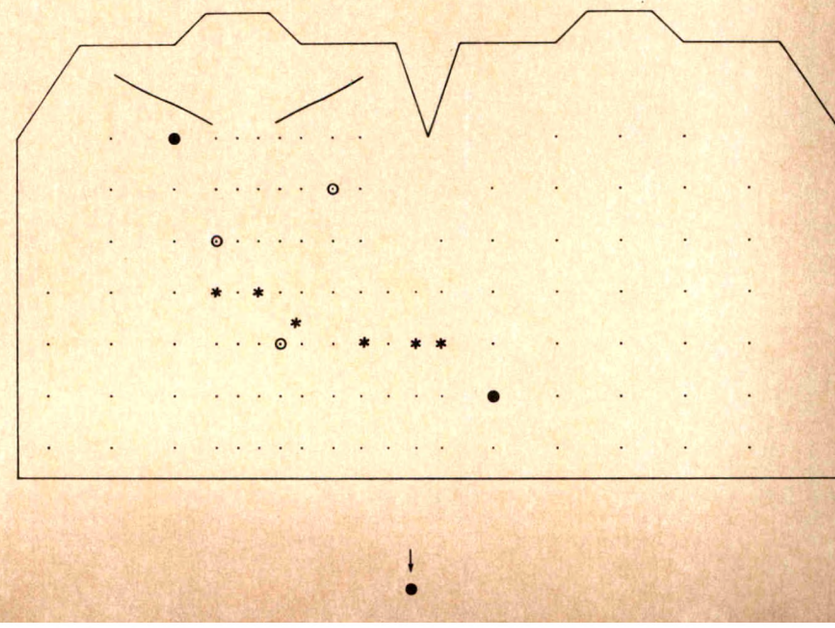

FIGURE 3. Schematic unfolded thorax. **Small dots** represent the electrode sites at which 120 electrocardiograms were simultaneously recorded, **small stars** the position of the precordial leads V_1 to V_6, **open dots** the electrode sites where electrocardiograms for maximal signal representation can be recorded and **black dots** the positions with maximal diagnostic information for the separation of normal subjects from patients with myocardial infarction.

unlikely candidates (e.g., lead 77), were selected. The essence of multivariate analysis is to reject redundancy when present and to combine variables that contribute independently to the overall classification. Therefore, all leads and all measurements must be analyzed.

Feature extraction from body surface potential maps: Although time-normalized QRS and ST-T waveforms can be considered adequate for the diagnostic sampling of electrocardiographic signals if they are represented by samples taken at 8 equal intervals,[8,9] we found that 8 QRS samples did not include some instances with maximal discriminant indexes. A separate study was conducted by adding peak QRS measurements to the already available QRS variables. No difference in the end performance was observed. As for the selected features, the bulk of the discrimination is achieved on the basis of voltage criteria (near-maximal amplitude as in 6/8 ST-T and 4/8 QRS). More subtle differences (3/8 ST-T or 2/8 QRS) show up in later steps.

Lead selection, lead subsets, and signal versus diagnostic information: The best leads originate from peripheral areas; their choice was not critical, because several leads in the same clusters showed similar abilities. Restricting the analysis to the 3 best leads did not significantly alter the diagnostic results, because most of the separation was achieved with the first 3 steps.

Finally, the discrepancy between optimal signal representation and optimal diagnostic representation for lead subsets has been illustrated earlier (Table IV, Fig. 3). In view of these results, the strategy for the selection of lead subsets will differ whether the former or the latter representation is sought. Optimal subsets for estimating total body surface potential distributions have been proposed by Barr et al[1] and later by Lux et al.[3,10] Their subsets, consisting of 24 and 32 leads, respectively, were optimal in the sense of least-mean-squared error for the representation of electrocardiographic signals at unmeasured sites.

The present study focuses mainly on selecting the smallest subset of optimal leads and features for separating normal subjects from patients with MI, irrespective of the site of the infarcts. The selected subset was arrived at on the basis of optimal diagnosis, not of optimal signal representation.

Extending the method to new groups may produce a lead set that is satisfactory for all diagnostic purposes or, more likely, different lead sets for different purposes. Lead sets that have optimal diagnostic ability may not account for, or allow, the reconstruction of the whole map, but they will preserve the map's practical information content.

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Assessment of Left Ventricular Aneurysm Resectability by Two-Dimensional Echocardiography

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Mortality of surgical resection of a left ventricular (LV) aneurysm is largely determined by size and function of nonaneurysmal or residual myocardium. A residual myocardial index was determined using 2-dimensional echocardiography (2-D echo) in 56 consecutive patients scheduled for LV aneurysmectomy, and these results were correlated with surgical outcome. The index was calculated using 3 apical cross sections: the 2- and 4-chamber views and the long-axis view. These views were recorded at mutual angles of 60°. In each view the end-diastolic length of normally moving endocardium of the 2 opposite walls was expressed as a fraction of the end-diastolic LV long axis. The index was assessed by averaging the 6 ratios obtained. In 41 survivors the index ranged from 40 to 71% (mean ± standard deviation 53 ± 7.8) and in 15 nonsurvivors from 29 to 67% (mean 38 ± 8.5, $p < 0.01$). With 1 exception, this echocardiographic index sharply separated survivors from nonsurvivors. The lower limit to survive aneurysmectomy was 40%.

(Am J Cardiol 1985;56:857–860)

Left ventricular (LV) aneurysm is a common complication of acute myocardial infarction. The incidence of postinfarction aneurysm reportedly varies between 10 and 38%.[1–7] Resection of an LV aneurysm in symptomatic patients may lead to a significant improvement in a functional class.[8–14] However, the rest of operative mortality may be high; mortality rates as high as 50% have been reported.[15–18] Thus, appropriate patients must be selected for this procedure. Until recently little agreement existed concerning invasive predictive measurements such as cardiac output, ejection fraction and LV end-diastolic pressure.[14,19,20] More recent studies, however, have shown that the postoperative results of LV aneurysmectomy are largely determined by the size and function of the nonaneurysmal or residual myocardium.[21–23] We examined whether patients most likely to survive LV aneurysmectomy could be identified by assessing the extent of residual myocardium by 2-dimensional echocardiography (2-D echo).

Methods

The study comprised 56 consecutive patients selected to undergo resection of an LV aneurysm secondary to coronary artery disease. There were 44 men and 12 women, mean age 52 ± 18 years. Seventeen patients (30%) underwent operation within 4 weeks after infarction. Almost all patients had 2 or more symptoms, including angina pectoris, congestive heart failure or ventricular tachycardia. The predominant indication for surgery of the whole group was congestive heart failure in 39 patients, refractory ventricular tachycardia in 10 and severe angina pectoris in 7. Congestive heart failure was the main indication in 13 of 17 patients (76%) who underwent aneurysmectomy within 4 weeks after infarction, and in 26 of 39 patients (67%) who underwent operation later. An aneurysm was documented in all patients by both cineangiography and 2-D echo and was defined by both methods as a well demarcated bulge in the contour of the LV wall during both diastole and systole and dyskinesia or akinesia.[24]

Two-dimensional echo was performed with use of a wide-angle, commercial mechanical sector scanner (ATL 300 or Ekosector 10A). All patients were studied in the left lateral decubitus position, and a standard echocardiographic approach was performed in which multiple LV parasternal long- and short-axis views were obtained as well as the apical 2- and 4-chamber views and the apical long-axis view.[25] These 3 apical cross sections were applied to assess the size of the residual myocardium. To improve spatial orientation of this part of the left ventricle, we fixed a calibrated ring containing oil and an air bubble to the body of the transducer. This device guarantees a mutual angle of 60° between the 3 apical cross sections.[26] Figure 1 is a schematic diagram of how we calculated the residual myocardium of the left ventricle with an apical aneurysm. After reviewing each cross section in real-time, slow-motion and still-frame formats, the end-diastolic length of the normally moving endocardium of each of the 6 walls of the left ventricle was estimated and expressed as a fraction of the end-diastolic long-axis length of the left ventricle. A residual myocardium index was then assessed by averaging the 6 ratios obtained and multiplying this by 100%. In the schematic example in Figure 1 the index calculated was 55% (see also Fig. 2).

Images were recorded on videotape and later analyzed by 2 observers who were blinded to each other's interpretation

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methods

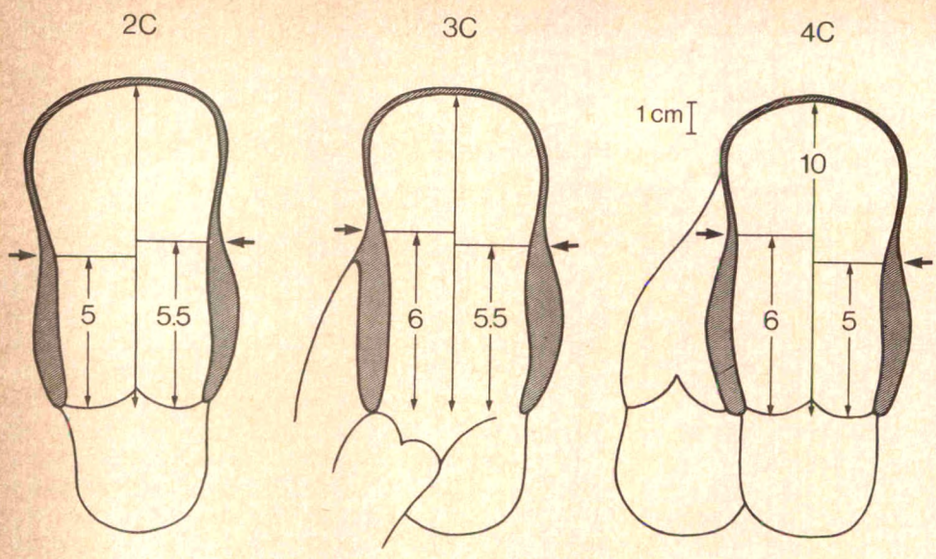

FIGURE 1. Method of evaluating the residual myocardial index of the left ventricle (RMI_{LV}). **Black arrows** indicate the separation between the normally moving endocardium and the apical aneurysm. The end-diastolic length of the normally moving endocardium of each of the 6 walls was expressed as a fraction of the end-diastolic long-axis of the left ventricle. 2C = 2-chamber view; 3C = apical long-axis or 3-chamber view; 4C = 4-chamber.

$$RMI_{LV} = \frac{\left(\frac{5}{10}+\frac{5.5}{10}\right)+\left(\frac{6}{10}+\frac{5.5}{10}\right)+\left(\frac{6}{10}+\frac{5}{10}\right)}{6} \cdot 100\% = 55\%$$

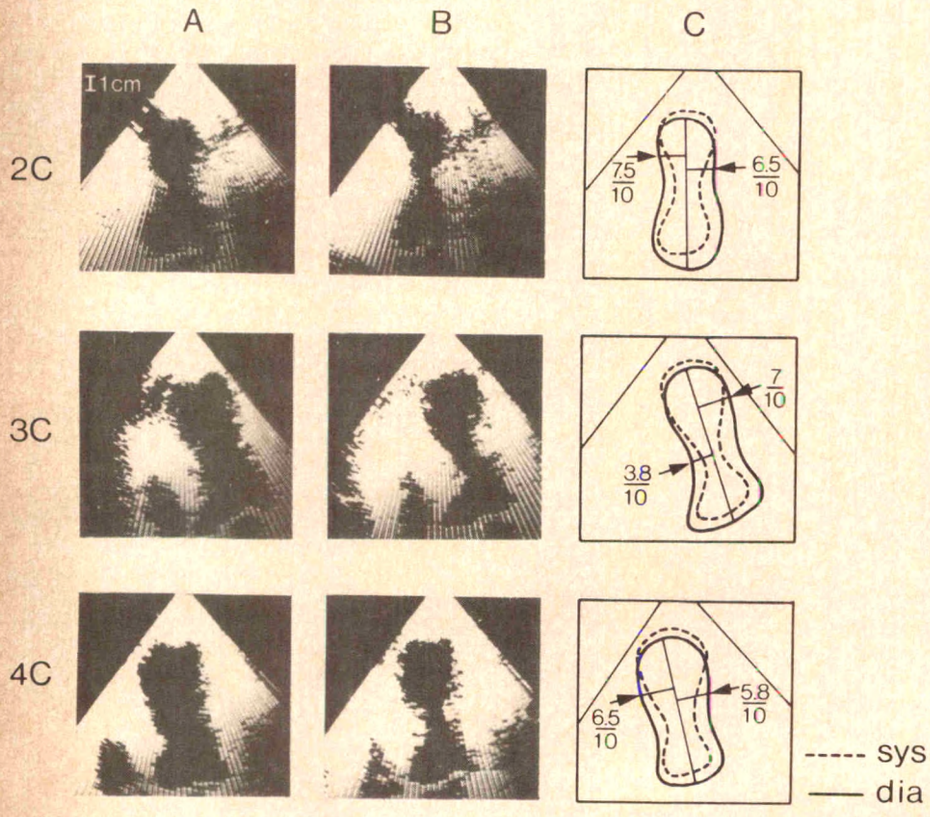

FIGURE 2. End-diastolic (**A**) and end-systolic (**B**) stop frames of a patient with an apical aneurysm. The line drawing (**C**) shows the endocardial outlines at end-systole (sys) and end-diastole (dia). The index in this patient was 61%. Other abbreviations as in Figure 1.

$$RMI_{LV} = \frac{1.4+1.08+1.23}{6} \cdot 100\% = 61\%$$

and the surgical outcome. Interobserver variation was low (r = 0.95). Disagreement was finally resolved by consensus upon repeat review of the recordings.

Results

Studies suitable for analysis were recorded in all 56 patients. The aneurysm was located at the anteroapical wall of the left ventricle in all but 1 patient, who had a circumscript but large basal aneurysm of the inferoposterior wall. The echocardiographic and cineangiographic site of aneurysm correlated closely.

Surgical mortality: Fifteen of the 56 patients (27%) who underwent aneurysmectomy died within 30 days of surgery. Nine of these 15 (60%) underwent operation within 4 weeks after infarction. The surgical mortality of this group was much higher than those who underwent operation later: 9 of 17 (53%) vs 6 of 39 (15%) ($p < 0.05$). Of the 15 patients who died, 13 (87%) died at the time of surgery or within 1 week after surgery. Ten of 13 patients died as a result of pump failure and 2 from refractory ventricular arrhythmias. Two patients died suddenly out of hospital.

Additional surgical procedures: In 12 of 15 nonsurvivors (80%) and 36 of 41 survivors (88%), respectively, 2.1 ± 0.6 (mean ± standard deviation) and 2.0 ± 0.7 bypass grafts were placed. Mitral valve replacement was performed in 3 nonsurvivors (20%) and in 6 survivors (15%). None of these differences was significant.

Residual myocardial index: The residual myocardial index of the whole group ranged from 29 to 71%. In the 15 nonsurvivors the index ranged from 29 to 68% (mean 38 ± 8.5%) (Fig. 3). The index of the 41 survivors ranged from 40 to 71% (mean 53 ± 7.8%) ($p < 0.001$ vs nonsurvivors).

All but 1 of the 15 nonsurvivors had an index of less than 40%. One patient had an index of 68%; this patient had a circumscript but large posterobasal aneurysm and died soon after operation from intractable ventricular arrhythmias.

Clinical improvement: The functional class (New York Heart Association[27]) after surgery was assessed in 29 patients who underwent operation primarily for congestive heart failure. The mean functional class was 3.7 ± 0.5 preoperatively and decreased to 2.3 ± 0.7 postoperatively ($p < 0.001$) (Fig. 4). Nineteen patients improved by 1 functional class and 9 by 2 functional classes. One patient in class IV improved by 3 functional classes.

Discussion

Because aneurysmectomy can lead to relief of symptoms in patients with an LV aneurysm, various invasive measures have been examined for their prognostic value. Of these, the size and function of the nonaneurysmal or residual myocardium has recently been shown to be very useful. Noninvasive determination of the residual myocardium may be clinically important in managing patients with LV aneurysm. Dillon et al[28] using M-mode echocardiography, showed that the LV dimension at the level of the base and papillary muscles could provide information about a patient's suitability for aneurysmectomy. Two-dimensional echo,

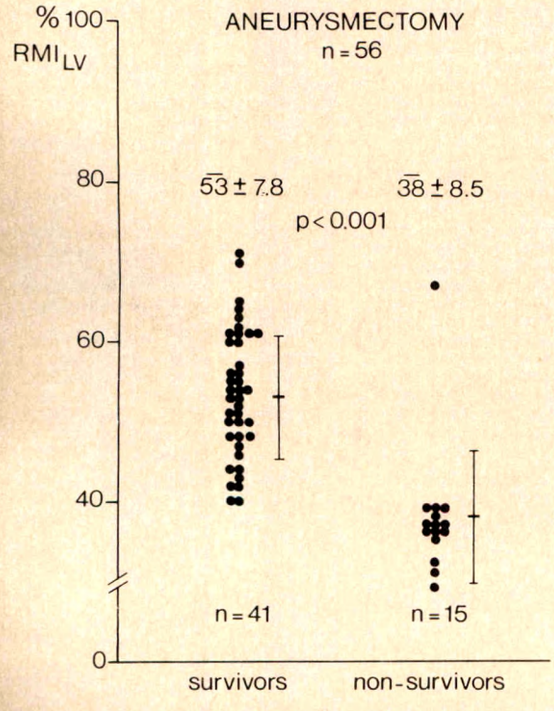

FIGURE 3. Comparison of the residual myocardial index of the left ventricle (RMI_{LV}) with surgical outcome in 56 patients who underwent aneurysmectomy. Except for 1 patient there is a sharp separation between survivors and nonsurvivors. Values are mean ± standard deviation.

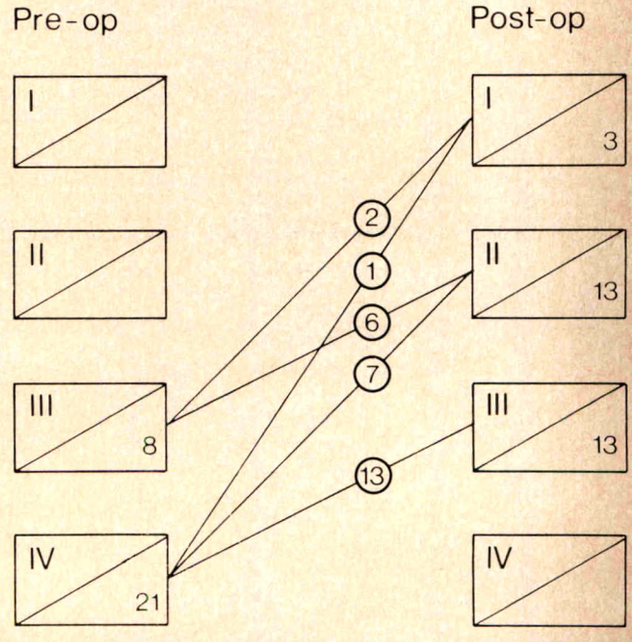

FIGURE 4. Preoperative and postoperative functional class (New York Heart Association criteria) of the 29 patients who underwent operation primarily for congestive heart failure. All patients improved by at least 1 functional class.

in contrast, permits study of the entire LV wall in detail, and therefore is ideally suited for noninvasive assessment of the residual myocardium. Unique information can be obtained about the ventricular septum. This part of the left ventricle is very often involved in an aneurysm and is often obscured on cineangiography by an apical aneurysm. Moreover, the method proposed was applicable in all of our patients.

Surgically mortality: Fifteen patients died after aneurysmectomy. This mortality rate is somewhat higher than that recently reported.[12] This can be explained by the urgent nature, i.e., soon after infarction, of reconstruction in 9 of these patients (67%). In patients undergoing aneurysmectomy soon after infarction the mortality rate is reported to be as high as 50%.[16,19,20] Although mitral valve replacement, in this respect, is usually associated with a high mortality, this additional procedure was not related to the mortality rate in our population.[29] Additional bypass grafting also was not related to the mortality rate. This is consistent with the results of Lee et al.[21] The prognostic value of the extent of coronary artery disease is still controversial.[14,21] The number of bypass grafts in our nonsurvivors was not significantly higher (2.1 ± 0.6 vs 2.0 ± 0.7).

Residual myocardium: Barrett et al[30] reported that an index of the residual myocardium assessed by 2 apical cross sections could predict the 6-month mortality in medically treated patients. Their index was highly related to the presence or absence of congestive heart failure. They could not precisely define the lower limit of surgically acceptable residual myocardium owing to the limited number of patients (12). Except for 1 patient, all of the nonsurvivors in our group had a residual myocardium index of the left ventricle of 39% or less. Thus, the lower limit of the residual myocardium index to survive surgical resection of an aneurysm was 40%. These results must be confirmed in a prospective study.

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Relation Between Heart Rate and QT Interval in Exercise-Induced Myocardial Ischemia

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The relation between heart rate and QT interval during dynamic upright exercise on a bicycle ergometer was investigated in control subjects (n = 18) and in patients with coronary artery disease (CAD), stable angina on effort, and angiographically documented significant coronary stenoses (n = 23). Both groups had a significant negative linear relation between heart rate and QT, with a higher correlation coefficient in control subjects (r = −0.78) than in patients with CAD (r = −0.64). This response may be a result of the nonhomogeneous response to ischemia in patients with CAD, particularly with regard to the different impact of exercise-induced ischemia.

When the 2 regression lines were compared, a flatter slope was found in the CAD group ($p < 0.001$) as a consequence of a faster decrease in the QT-increasing rate in control subjects. It is suggested that in control subjects exercise-induced increase in adrenergic tone causes a rapid and relevant decrease in QT-interval duration. In the CAD group, exercise-induced ischemia relatively prolonged the QT interval; this may have been the result of an impairment of myocardium in response to catecholamines release during exercise or the consequence of a direct effect of exercise-induced ischemia prolonging the duration of myocardial tension. **(Am J Cardiol 1985;56:861–862)**

Exercise induces several changes in the QRS-T pattern in patients with coronary artery disease (CAD), but their significance is not fully understood. The assumption that in the ischemic heart, electrical systole as measured by the QT interval (reflecting within limitation the duration of depolarization and repolarization[1]) is prolonged, remains controversial.[2–5]

Methods

Forty-one male volunteers investigated for chest pain were enrolled in the study. They underwent diagnostic coronary angiography. Eighteen patients, mean age (± standard error of the mean) 51 ± 4 years (range 37 to 59), had normal coronary arteries and they served as control subjects. The other 23 subjects, mean age 53 ± 4 years (range 35 to 60), had 70% or greater stenosis of at least 1 major coronary artery. Old myocardial infarction (older than 8 months) was present in 6. All of these CAD patients had positive stress test responses (significant ST depression[3] with chest pain or dyspnea or both). Medical treatment was progressively reduced and discontinued at least 1 week before stress test. Upright exercise was performed in the morning on a bicycle ergometer, with an initial work load of 50 W/min, and increased stepwise by 25 W/min every 2 minutes. Exercise end points were chest pain or dyspnea, 3 mm of ST depression below the value of rest, or attainment of maximal heart rate (HR). A standard 12-lead electrocardiogram was recorded at rest, at each step, at peak exercise and every minute during recovery at a paper speed of 25 mm/s using Marquette CASE equipment. This system minimizes baseline fluctuations of the electrocardiogram and facilitates QT measurement. QT was measured blindly by a trained cardiologist on lead II on 4 beats and averaged; mean HR was derived from the RR interval preceding each considered beat. To avoid miscalculation of QT because of P- or U-wave inclusion,[6] the end of the T wave was measured, whenever necessary, at the intersection between the isoelectric line and the tangential to the terminal limb of the T wave.[7] The correlation between HR and QT was sought by linear regression analysis,[8] considering QT and HR collected at each exercise step; data from the rest and recovery period were excluded. There were 69 entries for control subjects (3 to 4 per subject) and 71 for CAD patients (range 2 to 4). Differences between the regression lines were analyzed by the appropriate t test.[8] In control subjects, mean exercise tolerance was greater; therefore, we excluded data collected in control subjects for workloads greater than 125 W/min, the maximal load attained by CAD patients.

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Results

The intraobserver error for QT-interval measurement was estimated as 4 ms, or approximately 1% of the mean QT interval. Baseline, data at rest were similar (mean ± standard deviation of HR, QT and QTc in control subjects and CAD patients were: 82 ± 11, 338 ± 27, 394 ± 29; 78 ± 10, 348 ± 23 and 395 ± 21, respectively). There was a significant correlation between HR and QT in the 18 control subjects: QT(ms) = 451 − 1.36 HR, r = −0.78, $p < 0.001$ (Fig. 1). A significant correlation between QT and HR was also found in the 23 CAD pa-

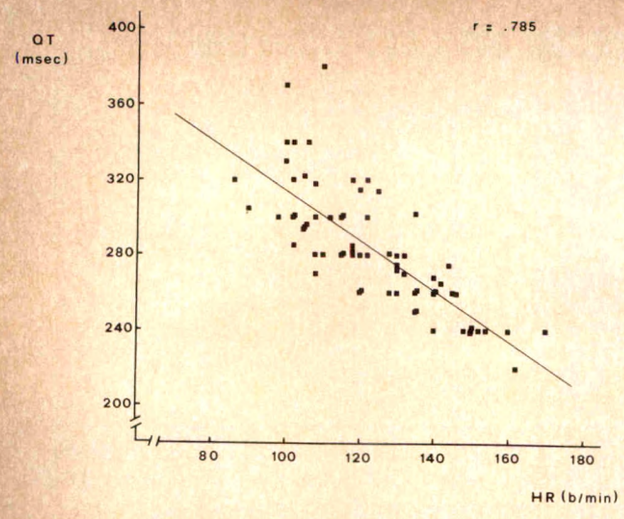

FIGURE 1. Relation between heart rate (HR) and QT interval (QT) during exercise in control subjects (n = 18). b = beats.

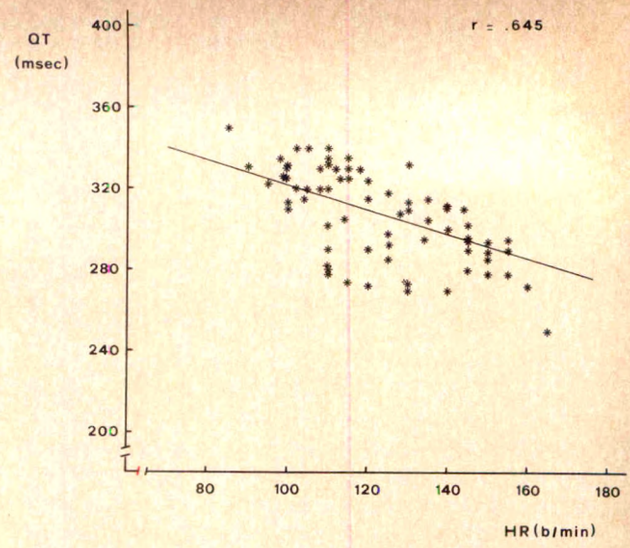

FIGURE 2. Relation between heart rate (HR) and QT interval (QT) during exercise in patients with coronary artery disease (n = 23). b = beats.

tients: QT(ms) = 396 − 0.73 HR, r = −0.64, p <0.001 (Fig. 2). However, the slopes of 2 regressions differed significantly (F = 12, p <0.001); this difference suggested that in CAD patients, similar increases in HR induce smaller decreases in QT duration.

Discussion

HR is an important determinant of the QT interval duration. The exercise-induced QT shortening is related not only to the increase in HR but also to the independent catecholamine activity.[9,10] In the present study, during exercise, QT decreased linearly while HR increased in normal control subjects as well as in CAD patients; however, the rate of QT shortening with HR increase was higher in control subjects than in CAD patients. This finding might be related to exercise-induced myocardial ischemic QT prolongation when the duration of myocardial tension was increased[11] or it may be related to an impairment in cardiac response to exercise-induced catecholamine release.[12,13] Moreover, β-adrenergic blockade was observed to blunt the QT changes in relation to HR variations during exercise.[10] In our study, the HR-QT correlation coefficient was smaller in CAD patients than in control subjects; this may be the result of nonhomogeneous development of myocardial ischemia during exercise; only ischemic regions will have an impaired responsiveness to catecholamines and the QT response to exercise will be relatively erratic. Since the more strenuous the exercise the greater the enhancement in sympathetic activity,[14] the larger difference between the 2 groups in HR-QT relation at the highest level of workload is the consequence of the greater catecholamine-induced QT reduction in control subjects compared with CAD patients. In these CAD patients, sensitivity to catecholamines of ischemic myocardium is reduced and QT interval decreases less. We studied well defined, selected populations (normal subjects and CAD patients with abnormal stress test); therefore, in a less defined, mixed population the effect of HR on QT may be less striking.

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Effects of Oral Amiodarone on Rate-Dependent Changes in Refractoriness in Patients with Wolff-Parkinson-White Syndrome

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The refractory periods during cardiac pacing were studied in 13 patients with the Wolff-Parkinson-White syndrome. The right atrial and right ventricular refractory periods and refractory period of the accessory pathway (anterogradely and retrogradely) were studied at 2 pacing cycle lengths before and after therapy with oral amiodarone (8,400 to 11,200 mg given in 4 to 6 weeks). The right atrial and right ventricular effective refractory period shortened significantly when the pacing rate was increased during the control study, and also after oral amiodarone administration. The anterograde and retrograde effective refractory period of the accessory pathway also shortened significantly at control study, but not during treatment with oral amiodarone. This indicated that amiodarone blunted the rate-dependent shortening in the refractory period of the accessory pathway. The rate-dependent increase in refractoriness of the accessory pathway could not be predicted or determined in all patients. In 5 patients a rate-dependent increase in the effective refractory period of the accessory pathway was observed in the anterograde direction and in 3 patients in the retrograde direction while they were receiving oral amiodarone therapy. When these data were correlated with the mode of induction and termination of tachycardia, however, a possible effect was found in only 1 patient. Further investigation of new antiarrhythmic drugs should include the development of components resulting in a reliable and predictable increase in refractoriness when the heart rate increases. This would result in prompt termination of reentrant tachycardia by creating block for the circulating impulse.

(Am J Cardiol 1985;56:863–866)

In the human heart the atrial, ventricular and His-Purkinje tissues react with a shortening of their refractory period when the heart rate increases during cardiac pacing. In contrast, the refractory period of the atrioventricular (AV) node lengthens during a pacing-induced increase in cardiac frequency.[1,2] In patients with the Wolff-Parkinson-White syndrome (WPW) who frequently suffer from either a circus movement tachycardia or atrial fibrillation, the relation between heart rate and the duration of the effective refractory period of the accessory pathway is clinically important. The duration of the refractory period of the accessory pathway can decrease, increase or stay the same during a pacing-induced increase in heart rate.[3] In WPW syndrome, when heart rate increases, it would be desirable to have lengthening of the refractory period of the accessory AV pathway, which determines the ventricular rate during atrial fibrillation and of the tissues incorporated in the circuit of circus movement tachycardia. This would protect the ventricle against very high ventricular rates during atrial fibrillation and facilitate spontaneous termination of circus movement tachycardia. Lengthening of the duration of the refractory period on increasing the heart rate would therefore be a very desirable effect of antiarrhythmic drugs. We report on the effects of amiodarone on rate-dependent changes in refractory periods in 13 patients with WPW syndrome.

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Methods

Thirteen patients with WPW were studied. The first electrophysiologic investigation was performed without drug therapy and the second after 4 to 6 weeks of therapy with oral amiodarone (total dose 8,400 to 11,200 mg). Our methods of stimulation and recordings and our definitions of effective and

TABLE I Electrophysiologic Data at Control Study and During Oral Amiodarone Treatment

Pt	PCL (ms)	RAERP		RAFRP		RVERP		ANTERP AP		RETERP-AP		ShPCL-AP	
		C	Am	C	Am	C	Am	C	Am	C	Am	C	Am
1	600	220	250	270	280	220	210	260	270	220	250	170	200
	500	200	230	250	280	210	200	250	260	210	240		
2	600	190	240	240	280	210	240	240	290	...	...	200	400
	430	190	260	230	290	200	230	230	350	...	...		
3	600	190	220	210	240	220	240	270	290	220	320	250	280
	500	180	220	240	230	210	210	250	300	210	300		
4	680	220	230	260	300	220	230	340	400	330	340	470	600
	600	200	220	270	270	200	220	330	>600	290	330		
5	600	230	260	250	330	240	260	270	330	...	...	280	300
	430	200	250	210	320	220	210	220	320	...	...		
6	750	230	250	310	280	280	250	330	330	...	260	280	...
	430	220	210	270	260	220	210	280	270	...	290		
7	600	240	280	260	310	220	230	260	320	280	...	230	360
	430	250	260	270	300	190	210	270	260	240	...		
8	600	230	210	260	270	240	260	280	290	...	...	300	300
	430	200	210	230	260	230	210	270	280	...	...		
9	680	250	260	290	290	250	260	330	350	370	410	300	400
	430	250	250	270	280	230	240	300	350	320	470		
10	750	290	270	300	320	240	240	310	360	370	400	345	420
	500	280	240	290	310	200	210	290	380	360	500		
11	750	190	230	250	350	210	276	250	330	...	...	240	300
	500	210	240	250	300	200	240	240	290	...	...		
12	600	270	260	310	290	260	250	320	600	370	390	350	600
	430	250	290	310	310	240	270	310	>430	350	370		
13	500	220	220	230	250	200	220	250	340	...	...	300	360
	430	210	190	230	240	190	210	240	350	...	...		

Values are in milliseconds.

Am = amiodarone; ANTERP = anterograde effective refractory period of the accessory pathway; C = control; PCL = pacing cycle length; RAERP = right atrial effective refractory period; RAFRP = right atrial functional refractory period; RETERP-AP = retrograde effective refractory period of the accessory pathway; RVERP = right ventricular effective refractory period; ShPCL-AP = shortest atrial pacing cycle length with 1-to-1 conduction over the accessory pathway.

functional refractory period are given elsewhere.[3] Refractory periods of right atrium and right ventricle and anterograde and retrograde conduction and refractory period of the accessory pathway were studied by the extrastimulus technique using 3 pacing cycle lengths. At least 2 of the 3 pacing cycle lengths were the same in all patients in the two studies, allowing comparison of results. Regular atrial pacing at increasing rates was also performed to determine the shortest cycle length with 1-to-1 anterograde conduction over the accessory pathway. The anterograde refractory period of the accessory pathway was determined using an atrial site close to the atrial insertion of the accessory pathway. Patients in whom the anterograde refractory period of the accessory pathway could not be determined exactly, because it was shorter than the functional refractory period of the atrium, are not included in this study. In general, the duration of the refractory period of the AV node could not be determined in the patients studied.

Statistical analysis was performed using the paired and unpaired Student t test for continuous variables and the chi-square test for discrete variables. A p value <0.05 was considered significant.

Results

Table I gives the values for the right atrial (RA) effective and functional refractory period, the right ventricular (RV) refractory period, and the anterograde and retrograde effective refractory period of the accessory pathway before and during treatment with oral amiodarone. Results are given at 2 pacing cycle lengths. Also, the shortest atrial pacing cycle length followed by 1-to-1 anterograde conduction over the accessory pathway is shown.

Right atrium: For the whole group of patients the mean difference between pacing cycle length 1 and 2 was 75 ms, or 35 beats/min (mean 94 vs 129 beats/min). At control study the mean duration of the RA effective refractory period at pacing cycle length 1 was 228 ± 20 ms, vs 244 ± 20 ms during oral amiodarone ($p < 0.05$), and 218 ± 28 ms vs 236 ± 25 ms at pacing cycle length 2 (difference not significant [NS]). A rate-dependent lengthening of the RA effective refractory period was observed in 2 patients at control study (10 to 20 ms) and in 3 patients during oral amiodarone therapy (10 to 30 ms). Two patients had no rate-dependent change in the duration of the RA effective refractory period at control study, and 2 patients had no change during oral amiodarone treatment. Amiodarone prolonged significantly the duration of the RA effective refractory period at pacing cycle length 1, but not at pacing cycle length 2. Therefore, no significant change occurred in the rate-dependent behavior of the RA effective refractory period after amiodarone.

The mean RA functional refractory period was 264 ± 29 and 255 ± 26 ms at control study at pacing cycle length 1 and 2, respectively, and 291 ± 29 and 280 ± 26 ms after oral amiodarone administration. Amiodarone prolonged significantly the RA functional refractory period at pacing cycle lengths 1 and 2 ($p < 0.05$ and $p < 0.02$). The mean RA functional refractory period shortened significantly with oral amiodarone when the pacing cycle length was shortened ($p < 0.05$). Three patients showed an increase in the duration of the RA functional refractory period when the pacing cycle

length was shortened during control study (range 10 to 30 ms) and 2 patients during oral amiodarone (range 10 to 20 ms) (NS).

Right ventricle: The RV effective refractory period decreased significantly at control study when the pacing cycle length was shortened (231 ± 21 vs 210 ± 15 ms at pacing cycle length 1 and 2, respectively, $p < 0.001$) and also during treatment with oral amiodarone (243 ± 16 vs 220 ± 18 ms, $p < 0.01$). The RV effective refractory period did not change significantly during treatment with oral amiodarone at any pacing cycle length. No patient showed a rate-dependent increase in RV effective refractory period at control study, and only 1 patient after oral amiodarone (20 ms). The lack of prolongation of the RV effective refractory period is in contrast with previous observations.[4] This may be a dose-related phenomenon.

Accessory pathway: The duration of the anterograde effective refractory period of the accessory pathway decreased significantly at control study when the pacing cycle length was shortened (285 ± 34 vs 267 ± 31 ms, $p < 0.01$), but not during treatment with oral amiodarone (346 ± 80 vs 341 ± 89 ms). Amiodarone prolonged significantly the duration of the anterograde effective refractory period of the accessory pathway at both pacing cycle length 1 and 2 ($p < 0.01$ and $p < 0.01$, respectively). Therefore, when the whole group of patients was considered, amiodarone hampered a rate-dependent shortening of the anterograde refractory period of the accessory pathway. A rate-dependent lengthening of the anterograde effective refractory period of the accessory pathway was present in 1 patient at control study and in 5 patients during oral amiodarone therapy (10 to 200 ms). Another patient showed no rate-related changes in duration of the anterograde refractory period of the accessory pathway while receiving amiodarone ($p < 0.05$, control vs amiodarone).

At control study the retrograde effective refractory period of the accessory pathway shortened significantly when the pacing cycle length was shortened (308 ± 63 vs 282 ± 58 ms, $p < 0.01$), but not during treatment with amiodarone (338 ± 60 vs 357 ± 89 ms). Amiodarone significantly prolonged the duration of the retrograde effective refractory period of the accessory pathway determined at pacing cycle length 1 or 2. No patient had rate-dependent lengthening of the retrograde effective refractory period of the accessory pathway during control study, but 3 patients had it during treatment with oral amiodarone. For the whole group of patients, therefore, amiodarone lessened the rate-dependent shortening in the retrograde effective refractory period of the accessory pathway present during control study.

The shortest cycle length followed by 1-to-1 anterograde conduction over the accessory pathway increased significantly after amiodarone treatment (285 ± 73 vs 376 ± 115 ms, $p < 0.05$).

Observations during circus movement tachycardia (Table II): Circus movement tachycardia was induced in 12 patients during control study and in 9 patients during treatment with oral amiodarone. Inability to induce tachycardia after amiodarone was based upon the creation of ventriculoatrial block in the accessory pathway in 2 patients and a long retrograde effective refractory period of the accessory pathway in 1 patient (no. 10). The mean tachycardia cycle length increased significantly after oral amiodarone (307 ± 49 vs 396 ± 60 ms, $p < 0.01$). During control study circus movement tachycardia did not terminate spontaneously in any patient, but tachycardia terminated spontaneously in 6 patients during oral amiodarone treatment.

TABLE II Observations During Circus Movement Tachycardia Before and After Amiodarone

	Control		Amiodarone	
Pt	TCL (ms)	SPT	TCL (ms)	SPT
1	350	–	435	AP
2	360	–	450	AVN
3	385	–	460	–
4	280	–	NI	–
5	280	–	300	AVN
6	270	–	300	Subnodally
7	285	–	NI	–
8	210	–	NI	–
9	255	–	350	AP
10	NI	–	NI	–
11	320	–	460	–
12	340	–	400	–
13	350	–	410	AVN

AVN = atrioventricular node; AP = accessory pathway; NI = not induced; SPT = spontaneous termination; TCL = tachycardia cycle length; – = negative.

The site of block during spontaneous termination of tachycardia on oral amiodarone treatment was the AV node in 3 patients, between the His bundle and the ventricle in 1 patient, and retrogradely in the accessory pathway in 2 patients. Only 1 of the last 2 patients showed a rate-dependent lengthening of the retrograde effective refractory period of the accessory pathway during single test stimulation of the ventricle during oral amiodarone treatment. In the other patients who showed a rate-dependent lengthening of the retrograde effective refractory period of the accessory pathway on amiodarone, tachycardia terminated subnodally (patient 6) or could not be initiated (patient 10).

Discussion

In reentrant tachycardias antiarrhythmic drugs can exert their beneficial effects by preventing the initiating premature beat or by changing the properties of the reentry circuit and affecting the critical balance between conduction velocity and refractoriness required to initiate and sustain reentrant tachycardia. Most antiarrhythmic drugs have marked effects not only on the duration of the refractory period of cardiac tissues, but also on conduction velocity. As a result of the interplay between effects on refractoriness and conduction velocity, antiarrhythmic drugs may prevent tachycardias in some patients but facilitate the occurrence of tachycardia in others. An antiarrhythmic drug with no or minimal effects on conduction velocity, but marked effects on refractoriness in the reentry circuit,

and particularly one that induces a rate-dependent lengthening of refractoriness in the reentry circuit would approach the ideal antiarrhythmic drug against reentry. The rate-dependent lengthening in refractoriness in a part or the whole reentrant circuit would result in prompt termination of tachycardia by creating block in the circuit for the circulating impulse.

Amiodarone is a potent antiarrhythmic drug with marked effects on refractoriness.[4,5] We wondered whether the creation of a rate-dependent lengthening in refractoriness contributed to its antiarrhythmic action. Patients with WPW were chosen because reentry is the mechanism of circus movement tachycardia and determination of the effects of an antiarrhythmic drug on the different components of the reentry circuit is possible.

During a mean rate difference of 35 beats/min during cardiac pacing, amiodarone reduced a rate-dependent shortening in duration of the anterograde and retrograde effective refractory periods of the accessory pathway. Results were statistically significant when the whole patient population was considered. When this information was correlated with the mode of spontaneous termination of circus movement tachycardia in 6 patients while receiving treatment with oral amiodarone, a possible clinical correlation could be demonstrated in only 1 patient. Explanations for these findings are: (1) the inability to initiate circus movement tachycardia in 4 patients while receiving oral amiodarone; (2) the effects of amiodarone on the AV node, making this the weak link in the tachycardia circuit[4]; and (3) the possibility that spontaneous adrenergic discharge during tachycardia counteracts the effects induced by amiodarone on rate-related changes on refractory periods.[6,7] The effects of amiodarone on rate-related changes in refractoriness of the AV node could not be studied in these patients because of anterograde conduction over an accessory pathway.

How amiodarone influenced a r
shortening in refractoriness of the acc
during pacing is not clear. We could no
between the initial duration of the ant
rograde effective refractory period o
pathway and blunting of the rate-depen
in refractoriness. The location of the acc
patients age or gender, spontaneous he
or total amiodarone dose had no appa
this phenomenon. As far as we know
antiarrhythmic drugs on rate-related
fractoriness has not yet been evaluate
heart. Because of their theoretical and p
implications, we believe that in the eva
velopment of antiarrhythmic drugs, the
drugs on changes in refractoriness in the
onset of tachycardia must be evalu
Theoretically the ideal antiarrhythmic
ment of reentrant tachycardia should c
relation between heart rate and refra
would facilitate the spontaneous term
arrhythmia should tachycardia develo

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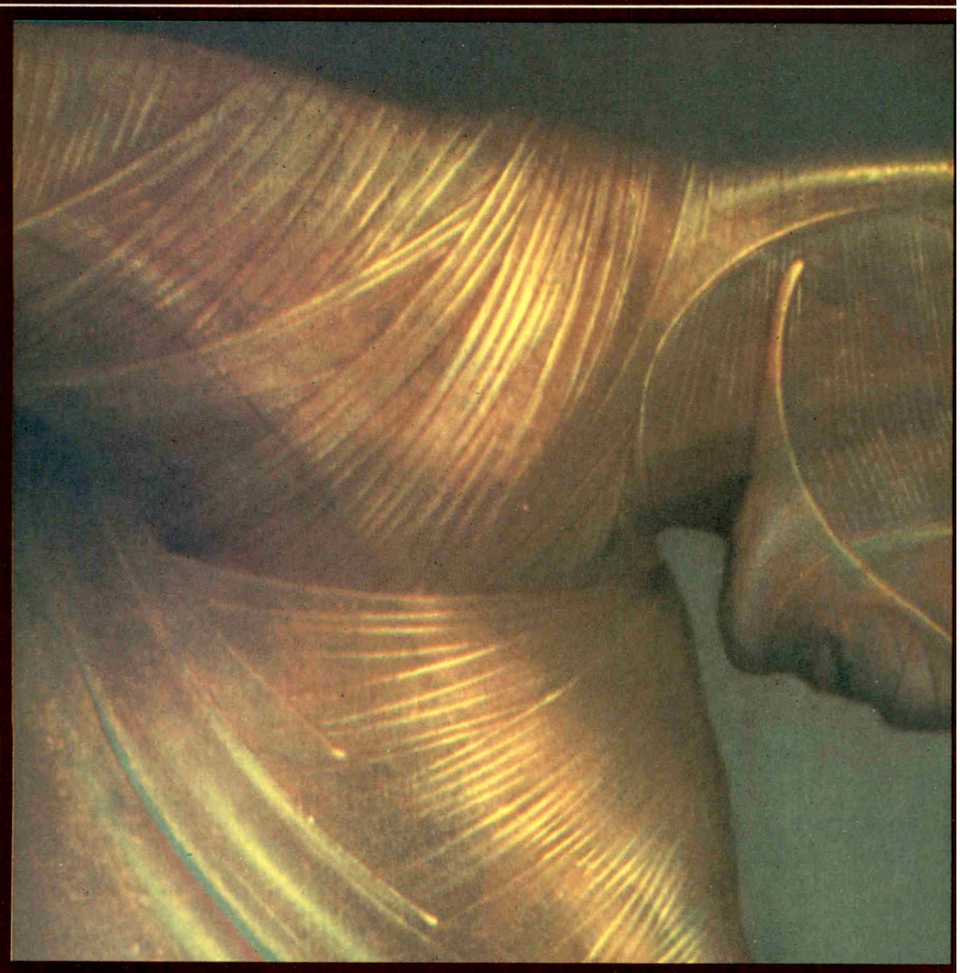
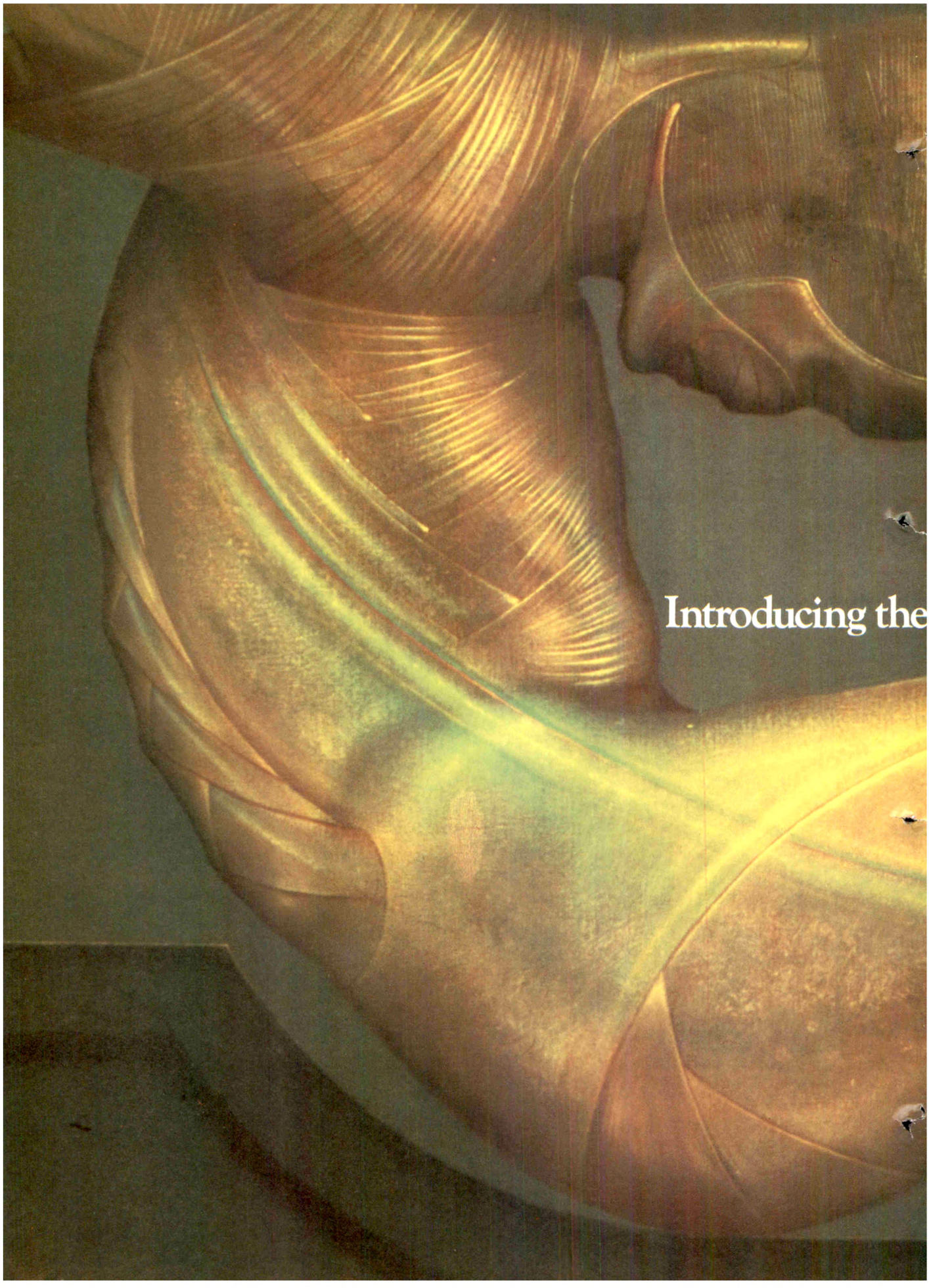
Between man and his medicine lies only a thin barrier...

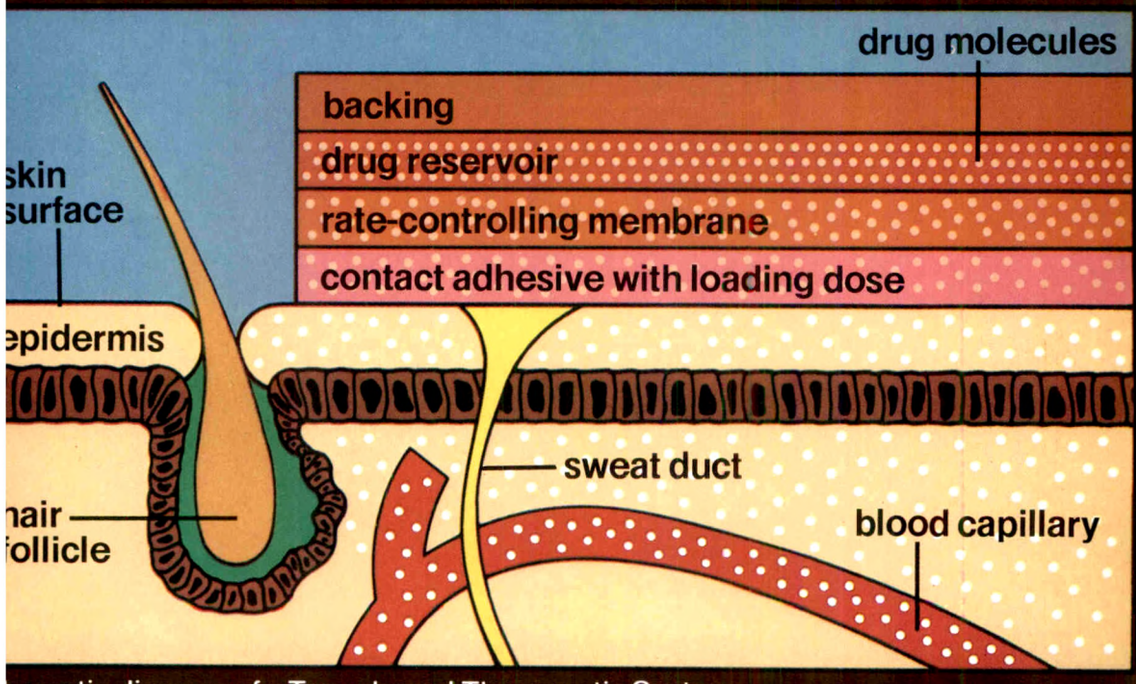


...the skin


Introducing the

irst once-a-week transdermal antihypertensive system
New Catapres-TTS®1,2,3
(clonidine) / Transdermal Therapeutic System
Hypertension
Please see brief summary of prescribing information on last page, including contraindications, precautions, and adverse reac

ontinuous 7-day transdermal delivery



hematic diagram of a Transdermal Therapeutic System
ced in contact with the skin.

New **Catapres-TTS®-1,2,3**

(clonidine) / Transdermal Therapeutic System

Hypertension

Actual size patches

THREE DOSAGE STRENGTHS...
Start with it in mild to moderate hypertension

- Convenient once-a-week dosage to aid compliance.
- Effective blood pressure control with or without a diuretic.
- Steady-state blood levels — without the peaks and valleys of oral forms.
- No diuretic-like biochemical effects.
- 24-hour blood pressure control 7 days a week.
- Central control of blood pressure.

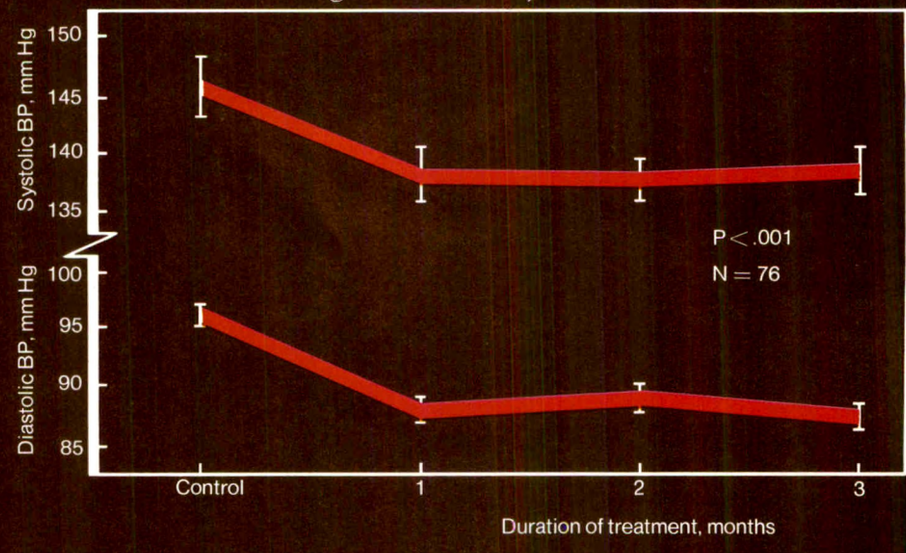
Most common side effects are dry mouth and drowsiness, which tend to diminish with time, and mild erythema and pruritus associated with 7-day skin occlusion. After a mean duration of treatment of 24 weeks, contact dermatitis was observed in 16% of patients. This condition resolved upon discontinuation of therapy.

Please see brief summary of prescribing information on last page, including contraindications, precautions, and adverse reacti

7 days of continuous therapy... a new age of complia

Documented long-term efficacy

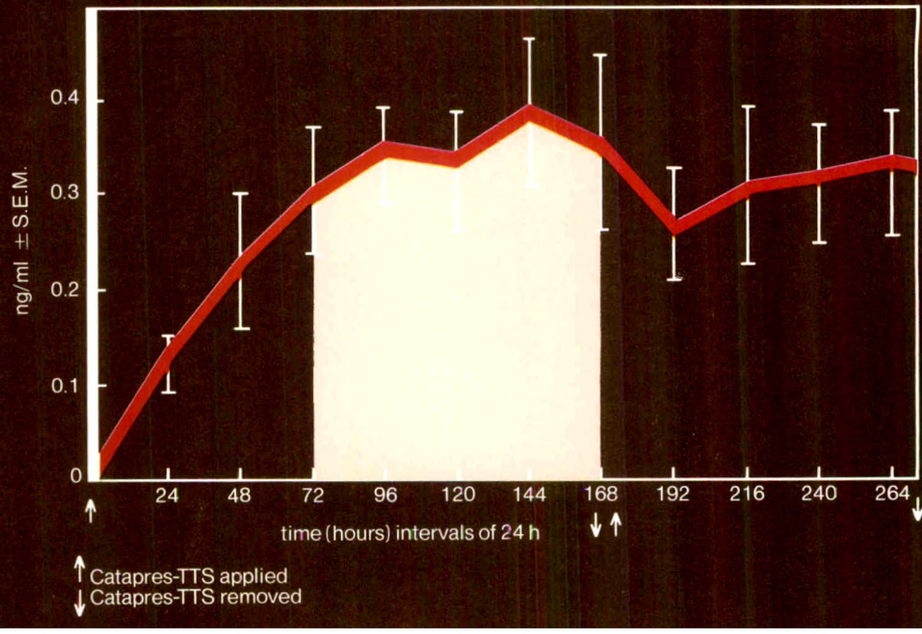
Systolic and diastolic BPs during control (placebo) and after 1, 2, and 3 months of treatment with clonidine administered transdermally. Values are means ± SEMs.[1]



Patch-to-patch applications

Steady-state blood levels— without the peaks and valleys of oral forms

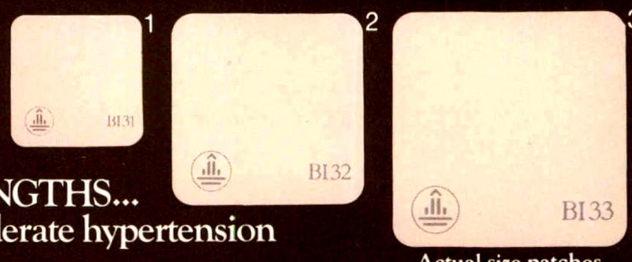
Mean (n = 5) clonidine plasma concentration (ng/ml)—3.5 cm² Catapres-TTS patch.[2]



New **Catapres-TTS®1,2,3**

(clonidine) / Transdermal Therapeutic System

Hypertension



Actual size patches

THREE DOSAGE STRENGTHS...
Start with it in mild to moderate hypertension

How to use Catapres-TTS®

Three Dosage Strengths for Individualized Therapy
Titrate to proper dosage with Catapres-TTS® alone

1. Start with #1. Replace with #2 and then #3 when necessary to achieve effective blood pressure control.
2. Catapres-TTS® is usually unaffected by showering or other routine daily activities. For some patients, use of an overlay is occasionally required to maintain adequate skin adherence.
3. Most common side effects are dry mouth and drowsiness, which tend to diminish with time, and mild erythema and pruritus associated with 7-day skin occlusion. Contact dermatitis was observed in 16% of patients (100 of 631) treated for a mean duration of 24 weeks. This condition resolved upon discontinuation of therapy.*

Rx

Catapres-TTS 1
x4 Sig:
apply once
weekly as
directed
Refill x2

*Please refer to **Precautions** in prescribing information if considering substitution of oral clonidine hydrochloride in patients who develop skin reactions during Catapres-TTS® therapy.

References:
1. Weber MA et al. Transdermal administration of clonidine for treatment of high BP. *Arch Intern Med* 1984; *144*:1211-13.
2. Data on file.

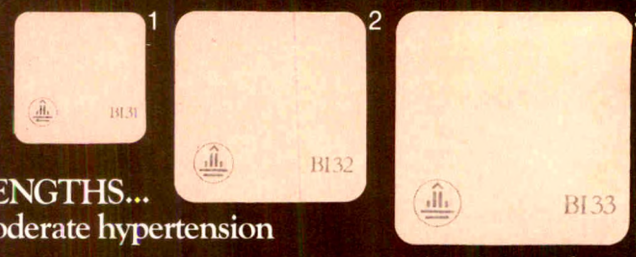
Please see brief summary of prescribing information on last page, including contraindications, precautions, and adverse reac

New

Catapres-TTS®1,2,3

(clonidine) / Transdermal Therapeutic System

Hypertension



THREE DOSAGE STRENGTHS...
Start with it in mild to moderate hypertension

Actual size patches

The first once-a-week transdermal antihypertensive system

Seven days of effective blood pressure control

- Convenient once-a-week dosage to aid compliance.
- Effective blood pressure control with or without a diuretic.
- Steady-state blood levels—without the peaks and valleys of oral forms.

Brief Summary of Prescribing Information

Contraindications: Catapres-TTS® (clonidine) should not be used in patients with known hypersensitivity to clonidine or to any other component of the adhesive layer of the therapeutic system.

Precautions: ***General:*** In patients who have developed localized contact sensitization to Catapres-TTS® (clonidine), substitution of oral clonidine hydrochloride therapy may be associated with development of a generalized skin rash.

In patients who develop an allergic reaction to Catapres-TTS® that extends beyond the local patch site (such as generalized skin rash, urticaria, or angioedema) oral clonidine hydrochloride substitution may elicit a similar reaction.

As with all antihypertensive therapy, Catapres-TTS® should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

Withdrawal: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in subjective symptoms such as nervousness, headache and sweating, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma, but such occurrences have usually been associated with previous administration of high oral doses (exceeding 1.2 mg/day) and/or with continuation of concomitant beta-blocker therapy. Rare instances of hypertensive encephalopathy and death have been reported.

An excessive rise in blood pressure following Catapres-TTS® discontinuance can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving beta-blockers and clonidine concurrently, beta-blockers should be discontinued several days before cessation of Catapres-TTS® administration.

Perioperative Use: As with oral clonidine therapy, Catapres-TTS® therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting Catapres-TTS® therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2 to 3 days after initial application of Catapres-TTS®.

Information for Patients: Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a potential sedative effect of clonidine. Patients should be cautioned against interruption of Catapres-TTS® therapy without a physician's advice. Patients should be advised that if the system begins to loosen from the skin after application, the adhesive overlay should be applied directly over the system to ensure good adhesion over its 7-day lifetime. Instructions for using the system are provided. Patients who develop moderate or severe erythema and/or localized vesicle formation at the site of application, or a generalized skin rash, should consult their physician promptly about the possible need to remove the patch.

Drug Interactions: If a patient receiving clonidine is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage. Clonidine may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives. Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 132-week oral carcinogenicity study in rats, clonidine hydrochloride produced no carcinogenic effects at doses up to 300 times the maximum recommended human dose of Catapres-TTS® on a mg/kg weight basis.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Reproduction studies performed in rabbits at doses up to 3.1 times the maximum recommended daily human dose of Catapres-TTS® have revealed no evidence of impaired fertility or harm to the fetus due to clonidine hydrochloride. Studies in rats and mice revealed that doses of 500 mcg/kg/day and higher are embryotoxic. One rat study at doses of 15 mcg/kg/day (0.33 times the maximum recommended daily human dose) exhibited embryotoxicity. There are no adequate and well-controlled studies in pregnant women. Although animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: As clonidine is excreted in human milk, caution should be exercised when Catapres-TTS® (clonidine) is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

Adverse Reactions: Most systemic adverse effects during therapy with Catapres-TTS® (clonidine) have been mild and have tended to diminish with continued therapy. In a 3-month, multiclinic trial of Catapres-TTS® in 101 hypertensive patients, the most frequent systemic reactions were dry mouth (25 patients) and drowsiness (12 patients).

Transient localized skin reactions, primarily localized pruritus occurred in 51 patients. Twenty-six patients experienced localized erythema. This erythema and pruritus were more common in patients utilizing an adhesive overlay for the entire 7-day treatment period. Allergic contact sensitization to Catapres-TTS® was observed in 5 patients.

In additional clinical experience, contact dermatitis was observed in 100 of 631 patients (about 16 in 100) treated for a mean duration of 24 weeks.

The following less frequent adverse experiences were also reported in patients involved in the multiclinic trial with Catapres-TTS®.

Gastrointestinal: Constipation (1 patient); nausea (1); and change in taste (1).

Central Nervous System: Fatigue (6 patients); headache (5); lethargy (3); sedation (3); insomnia (2); dizziness (2); and nervousness (1).

Genitourinary: Impotence/sexual dysfunction (2 patients).

Dermatological: Localized vesiculation (7 patients); hyperpigmentation (5); edema (3); excoriation (3); burning (3); papules (1); throbbing (1); blanching (1); and generalized macular rash (1).

In additional clinical experience involving 3539 patients, less common dermatologic reactions have occurred, where a causal relationship to Catapres-TTS® was not established: maculopapular skin rash (10 cases); urticaria (2 cases); angioedema involving the face (2 cases), one of which also involved the tongue.

Oro-otolaryngeal: Dry throat (2 patients).
In long experience with oral clonidine hydrochloride, the most common adverse reactions have been dry mouth (about 40%), drowsiness (about 35%) and sedation (about 8%). In addition, the following adverse reactions have been reported less frequently:

Gastrointestinal: Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; parotitis, rarely.

Metabolic: Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely.

Central Nervous System: Nervousness and agitation, about 3 in 100 patients; mental depression, about 1 in 100 and insomnia, about 5 in 1000. Vivid dreams or nightmares, other behavioral changes, restlessness, anxiety, visual and auditory hallucinations and delirium have been reported.

Cardiovascular: Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (i.e. conduction disturbances and arrhythmias) have been reported rarely.

Dermatological: Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.

Genitourinary: Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Other: Weakness, about 10 in 100 patients; fatigue, about 4 in 100; headache, and discontinuation syndrome, each about 1 in 100; muscle or joint pain, about 6 in 1000 and cramps of the lower limbs, about 3 in 1000. Dryness, burning of the eyes, dryness of the nasal mucosa, pallor, weakly positive Coombs' test, increased sensitivity to alcohol and fever have been reported.

How Supplied: Catapres-TTS®-1 (clonidine), Catapres-TTS®-2 (clonidine) or Catapres-TTS®-3 (clonidine) is supplied as 4 pouched systems and 4 adhesive overlays per carton.

Catapres-TTS®-1 or Catapres-TTS®-2 is supplied in a shipper of 3 cartons.

Consult package insert before prescribing.

CT-BPI-6/85

Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

(9/85) CT-2717

Evaluation by Serial Electrophysiologic Studies of an Abbreviated Oral Loading Regimen of Amiodarone

ELEANOR E. KENNEDY, MD, LYNDA E. ROSENFELD, MD, CRAIG A. McPHERSON, MD, and WILLIAM P. BATSFORD, MD

Optimal loading and maintenance regimens for amiodarone are undefined. Serial electrophysiologic testing was used in 25 patients with ventricular tachycardia to assess the adequacy of a 1-week oral loading regimen at 1,200 mg/day, to modify maintenance dosing at the conclusion of loading, and to evaluate the appropriateness of maintenance dosing after 2 months of therapy. During the loading period, highly significant ($p < 0.001$) increases occurred in the AH interval (88 ± 22 vs 120 ± 31 ms), HV interval (49 ± 10 vs 61 ± 11 ms), AV nodal Wenckebach cycle length (390 ± 92 vs 537 ± 147 ms), ventricular refractory period (247 ± 17 vs 276 ± 23 ms), mean ventricular tachycardia cycle length (254 ± 38 vs 298 ± 52 ms) and return cycle length (294 ± 55 vs 360 ± 87 ms). Ventricular tachycardia inducibility decreased in only a minority of cases, and when observed in association with a more than 10% increase in ventricular refractory period, resulted in a lower maintenance dose. After 2 months of maintenance therapy no additional change occurred in any of these parameters except for an increase in ventricular tachycardia cycle length (298 ± 52 vs 330 ± 65 ms, $p < 0.017$). Ventricular tachycardia inducibility again showed no consistent response. It is concluded that patients can be discharged after 1 week of therapy with oral amiodarone loading at 1,200 mg/day and that maintenance dosing modified by electrophysiologic assessment results in steady perpetuation of the cardiac amiodarone effect, as indicated by the time course of change in electrophysiologic variables consistently affected.

(Am J Cardiol 1985;56:867–871)

Because of its unusual pharmacokinetic characteristics,[1–4] optimal dosing with amiodarone is controversial. In particular, oral loading regimens have varied widely, with doses ranging from 600 to 1,400 mg/day and duration of loading ranging from 1 to 4 weeks.[5–9] This problem is fostered by the difficulty in applying standard methods of judging antiarrhythmic effect to amiodarone.[7–13] The effects of oral amiodarone on electrophysiologic variables have been well described[7,12–16] and are a direct bioassay of cardiac drug effect. The purposes of this prospective study were to determine whether a relatively abbreviated 1-week oral loading regimen resulted in substantial electrophysiologic change, and to determine whether, as opposed to a fixed dosing schedule, individual discharge dosing could be appropriately modified on the basis of electrophysiologic findings after the loading period.

Methods

Patients: The study group consisted of 25 consecutive patients with ventricular arrhythmias unrelated to acute myocardial infarction or other reversible phenomena and in whom control electrophysiologic study could be performed within 3 weeks of the start of amiodarone therapy. Clinical characteristics are detailed in Table I. All patients with nonsustained ventricular tachycardia (VT) had either syncope in association with nonsustained VT on Holter monitoring or long and frequent asymptomatic runs of nonsustained VT on electrocardiographic monitoring.

Amiodarone dosing regimen (Table II): Patients received an oral loading dose of 1,200 mg/day for 8 ± 2 days (mean ± standard deviation). An 800-mg loading dose, as well as a reduced maintenance dose, was used for patients 3 and 12 because of their weight (less than 55 kg). Patients were then discharged receiving reduced doses of amiodarone, most often given at 800 mg/day. Discharge doses of 400 to 600 mg/day were considered for patients with clinical sustained VT or nonsustained VT if at least 1 of the following criteria were met: (1) a gross decrease in VT inducibility accompanied by more than 10% increase in the ventricular refractory period (patients 2, 13, and 14), (2) a noninducible response in association with the clinical diagnosis of nonsustained VT (patients 13, 14 and 24), and (3) intolerable side effects (patient 3 and 13). Patient 1, whose clinical arrhythmia was nonsustained VT, was also discharged receiving 600 mg/day because his maximal response of 5 consecutive complexes of VT barely met our criteria for induced nonsustained VT (see later). All patients with primary ventricular fibrillation received 800 mg/day. After 2 months of therapy (69 ± 14 days), the dosage was reduced further (408 ± 158 mg/day) for long-term treatment.

Electrophysiologic studies: All patients underwent electrophysiologic evaluation in the control state 4 or more half-lives after discontinuation of all antiarrhythmic agents, after 1 week (8 ± 2 days) of oral amiodarone loading, and after

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TABLE I Clinical Characteristics

No. of patients	25
Age (yr)	58 ± 15
Male/female	17/8
Cardiac diagnosis	
Coronary artery disease	16
Dilated cardiomyopathy	5
Valvular heart disease	2
Right ventricular dysplasia	1
No known heart disease	1
Left ventricular ejection fraction (%)	33 ± 15
Clinical arrhythmia	
Ventricular fibrillation	5
Sustained ventricular tachycardia	9
Nonsustained ventricular tachycardia	11
Previous drug trials failed	3.3 ± 1.7

2 months (69 ± 14 days) of outpatient maintenance therapy. Patients were studied in the postabsorptive nonsedated state after they gave written informed consent. Multielectrode catheters were inserted percutaneously and positioned under fluoroscopic guidance. Recording and pacing sites included the high right atrium, His bundle area, right ventricular apex and coronary sinus. Surface leads I, II and V_1 were displayed simultaneously with intracardiac tracings and recorded on a VR-12 (Electronics for Medicine) recorder at a paper speed of 50 to 150 mm/s. Cardiac stimulation was performed with a programmed constant-current stimulator (World Precision Instruments) using rectangular pulses 1 ms in duration, delivered at twice diastolic threshold or 1.5 mA, whichever was higher.

Sinus cycle length, corrected sinus node recovery time, sinoatrial conduction time, AH and HV intervals, and refractory periods of the right atrium and right ventricle were measured according to standard techniques.[17,18] The maximal atrioventricular nodal Wenckebach cycle length was determined by incremental atrial pacing. The ventricular stimulation protocol consisted of (1) single, double and triple extrastimuli during spontaneous rhythm and at 2 or more paced cycle lengths, (2) single and double extrastimuli following a drive train with abrupt short-to-long cycle length changes,[19] and (3) brief bursts of rapid right ventricular pacing. The endpoints of stimulation were (1) induction of sustained VT, (2) induction of rapid nonsustained VT (mean cycle length 250 ms or less) of at least 10 consecutive complexes, or (3) ventricular refractoriness.[20] VT mean cycle length and return cycle length, the latter defined as the interval from the ventriculogram of the last programmed extrastimulus to the first VT complex, were measured in patients with induced VT lasting at least 5 consecutive complexes at all 3 studies.

Definition of induced ventricular responses: Sustained VT was defined as VT requiring pacing or external cardioversion for termination. Nonsustained VT was defined as VT of at least 5 consecutive complexes and reverting spontaneously to supraventricular rhythm. A noninducible response occurred when fewer than 5 consecutive VT complexes could be induced after completion of the stimulation protocol. A decrease in inducibility was defined as a change from sustained VT to either nonsustained VT or a noninducible response, or a change from nonsustained VT to a noninducible response.

Statistical methods: Analysis was performed using a Student 2-tailed paired t test. In accordance with the Bonferroni correction for multiple comparisons,[21] $p < 0.017$ was required for statistical significance. All values are given as mean ± standard deviation in milliseconds unless otherwise specified.

Results

The effects of amiodarone on electrophysiologic variables are summarized in Table III. There is a con-

TABLE II Individual Arrhythmia Diagnosis, Amiodarone Dosing Regimen, and Effect on Ventricular Refractory Period and Inducibility

Pt	Dx	Loading Dose (mg/day)	Loading Duration (days)	VRP (ms)			Inducibility		Discharge Dose (mg/day)
				C	1 wk	% Δ	C	1 wk	
1	NSVT	1,200	8	230	260	13	NSVT	NSVT	600
2	VT	1,200	7	270	330	22	NSVT	NI	400
3	VT	800	8	260	. . .	. . .	VT	VT	200
4	VT	1,200	7	. . .	260	. . .	NSVT	VT	800
5	VF	1,200	12	210	250	19	NSVT	NSVT	800
6	VT	1,200	7	240	260	8	VT	NSVT	800
7	NSVT	1,200	7	250	260	4	NSVT	NSVT	800
8	VT	1,200	9	280	290	4	VT	VT	800
9	VT	1,200	11	250	280	12	NI	NI	800
10	NSVT	1,200	7	240	250	4	NSVT	NSVT	800
11	VT	1,200	7	240	270	13	NSVT	NSVT	800
12	NSVT	800	7	260	300	15	NSVT	NSVT	400
13	NSVT	1,200	7	230	280	22	VT	NI	400
14	NSVT	1,200	8	260	300	15	NSVT	NI	600
15	VF	1,200	7	240	250	4	VT	NSVT	800
16	NSVT	1,200	8	280	280	0	NSVT	NSVT	800
17	VF	1,200	8	230	290	26	VT	NSVT	800
18	VF	1,200	7	250	290	16	NSVT	VT	800
19	VT	1,200	8	250	240	−4	VT	VT	800
20	VT	1,200	7	. . .	. . .	. . .	NSVT	VT	800
21	NSVT	1,200	7	230	300	30	NSVT	NSVT	800
22	VF	1,200	7	240	310	24	NSVT	VT	800
23	NSVT	1,200	7	240	290	21	NSVT	VT	800
24	NSVT	1,200	7	. . .	250	. . .	NI	NI	600
25	NSVT	1,200	7	. . .	250	. . .	NSVT	VT	800
Mean		1,168	8	247	276	14			696
± SD		± 109	± 1	± 17	± 23	± 10			± 183

C = control; Dx = arrhythmia diagnosis; NI = noninducible; NSVT = nonsustained ventricular tachycardia; SD = standard deviation; VF = ventricular fibrillation; VRP = ventricular refractory period; VT = sustained ventricular tachycardia; % Δ = percent change; . . . = not done.

TABLE III Effects of Amiodarone on Electrophysiologic Parameters

	C	1 Week	2 mo.	p Values (no. of patients) C vs 1 Week	1 Week vs 2 mo.	C vs 2 mo.
SCL	802 ± 144	877 ± 198	924 ± 170	NS (23)*	NS (23)	<0.001 (23)
CSNRT	359 ± 228	435 ± 323	433 ± 307	NS (19)	NS (21)	NS (19)
SACT	133 ± 54	155 ± 52	121 ± 47	NS (7)	NS (14)	NS (12)
AH	88 ± 22	120 ± 31	111 ± 25	<0.001 (23)	NS (23)	<0.001 (23)
HV	49 ± 10	61 ± 11	64 ± 13	<0.001 (24)	NS (25)	<0.001 (24)
WCL	390 ± 92	537 ± 147	541 ± 123	<0.001 (22)	NS (24)	<0.001 (24)
ARP	233 ± 37	280 ± 49	289 ± 46	<0.017 (13)	NS (14)	<0.005 (12)
VRP	247 ± 17	276 ± 23	284 ± 25	<0.001 (20)	NS (22)	<0.001 (20)
VTCL	254 ± 38	298 ± 52	330 ± 65	<0.001 (16)	<0.017 (16)	<0.001 (16)
RCL	294 ± 55	360 ± 87	368 ± 68	<0.005 (16)	NS (16)	<0.001 (16)

All values are expressed as mean ± standard deviation in milliseconds.
* $p < 0.05$, but not significant by Bonferroni correction requiring $p < 0.017$ for 3 comparisons.
ARP = atrial refractory period; C = Control; CSNRT = corrected sinus node recovery time; NS = not significant; RCL = return cycle length; SACT = sinoatrial conduction time; SCL = sinus cycle length; VRP = ventricular refractory period; VTCL = ventricular tachycardia cycle length; WCL = Wenckebach cycle length.

tinuous trend toward an increase in sinus cycle length over the treatment period (Fig. 1), which reaches statistical significance when the control and 2-month studies are compared ($p < 0.001$). There were no significant changes in corrected sinus node recovery time or sinoatrial conduction time (Fig. 1).

In contrast, the AH and HV intervals and Wenckebach cycle length increased ($p < 0.001$) during the loading period and remained stable thereafter during the maintenance phase (Fig. 2). Refractory periods of the atrium and ventricle also lengthened during amiodarone therapy (Fig. 3), and exhibited the same pattern as that followed by the AH and HV intervals and the Wenckebach cycle length.

VT cycle length increased after 1 week of amiodarone loading ($p < 0.001$), with a further increment ($p < 0.017$) occurring from 1 week to 2 months (Fig. 4). The return cycle length followed the predominant pattern, with a significant increase during loading, which was sustained at the same level during maintenance therapy.

Assessment of overall (Fig. 5) and individual (Table II) response to programmed right ventricular stimulation revealed no consistent pattern of change in inducibility. Although some patients showed a decrease in the level of VT inducibility with amiodarone relative to the control state, most did not. There was no striking change over time in the proportion of patients who had sustained VT, nonsustained VT or a noninducible response.

Toxicity and efficacy: Two instances of intolerable side effects occurred during loading (gastrointestinal and sinus node dysfunction) and 7 instances occurred during 14 ± 5 months of follow-up: 2 pulmonary, 3 gastrointestinal, 1 neurologic and 1 hepatic. Amiodarone therapy was discontinued in 1 patient with primary ventricular fibrillation, who had an unacceptable proarrhythmic response with a marked increase in the

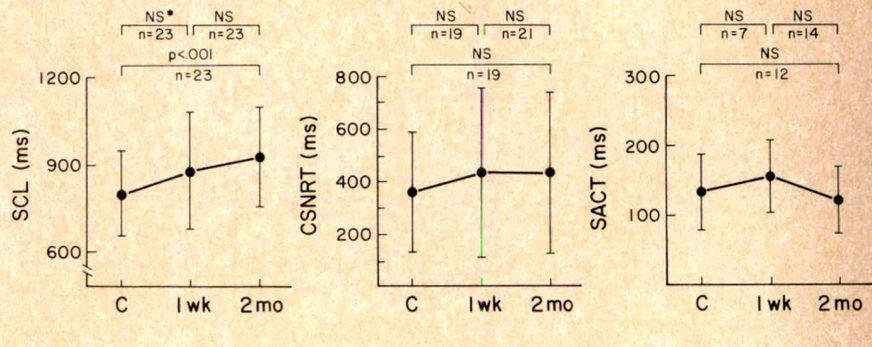

FIGURE 1. Sinus node functional testing in the control state, after 1 week of oral amiodarone loading, and after 2 months of maintenance therapy. All values are expressed as mean ± standard deviation. * $p < 0.05$ but not significant by Bonferroni correction; C = control electrophysiologic study; CSNRT = corrected sinus node recovery time; NS = not significant; SACT = sinoatrial conduction time; SCL = sinus cycle length.

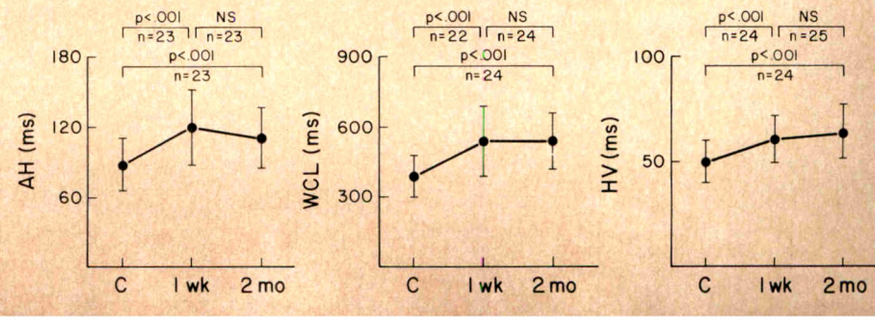

FIGURE 2. Atrioventricular conduction in the control state, after 1 week of oral amiodarone loading, and after 2 months of maintenance therapy. NS = not significant; WCL = Wenckebach cycle length.

ease of VT inducibility after 2 months of amiodarone therapy. Of the remaining 24 patients, 19 (79%) have remained free of arrhythmia recurrence.

Discussion

Two conclusions of direct clinical importance regarding amiodarone dosing are suggested by these data. First, significant electrophysiologic effects can be achieved after 1 week of oral loading with 1,200 mg/day. This finding is of clinical relevance because patients have previously been hospitalized for up to 4 weeks for amiodarone loading.[7,9] Because no arrhythmia recurred between 1 week and 2 months of therapy, patients generally can be discharged after a 1-week loading period in the absence of persistent spontaneous and severe arrhythmias.

Second, the extent of electrophysiologic change after loading may be useful in selecting the level of maintenance therapy. A decrease in VT inducibility, which previously has been suggested to have favorable prognostic implications with amiodarone,[22,23] prompted a lower discharge dose when associated with a more than 10% increase in ventricular refractory period. The increase in refractory period was required to lessen the possibility that the decrease in VT inducibility was an artifact of programmed ventricular stimulation nonreproducibility,[20] and to substantiate the role of amiodarone therapy in the decrease in VT inducibility in these individual cases, since amiodarone did not affect VT inducibility with any degree of consistency in the patient group as a whole.

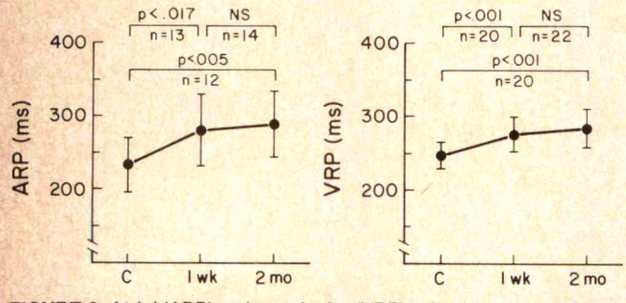

FIGURE 3. Atrial (ARP) and ventricular (VRP) refractory periods in the control state, after 1 week of oral amiodarone loading, and after 2 months of maintenance therapy. NS = not significant.

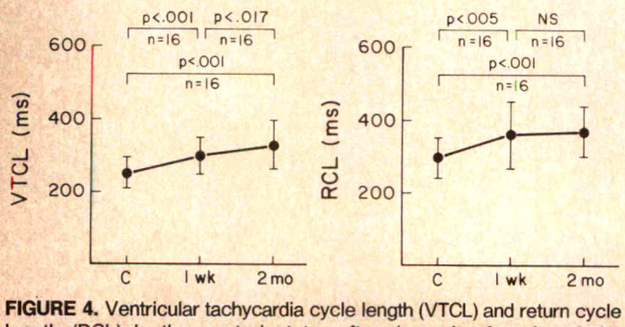

FIGURE 4. Ventricular tachycardia cycle length (VTCL) and return cycle length (RCL) in the control state, after 1 week of oral amiodarone loading, and after 2 months of maintenance therapy. NS = not significant.

Effect of amiodarone on electrophysiologic parameters: Unlike VT inducibility, many electrophysiologic variables were affected in a consistent manner by amiodarone. Sinus cycle length, AH interval, AV nodal Wenckebach cycle length, atrial and ventricular refractory periods and mean VT cycle length all increased, consistent with earlier studies.[7,12–16] The HV interval also lengthened, as observed by some[7,14] but not all previous investigators.[12,13]

With 2 exceptions, all consistently affected variables significantly increased during loading, and these increases were sustained, with no further major change during maintenance therapy. The more continuous increase in sinus cycle length and mean VT cycle length is consistent with observations by other investigators,[11,24] who noted more marked increases in these 2 measurements during chronic oral therapy than during acute intravenous therapy. Whether metabolite effect or slower penetration of a "deeper"[10] physiologic compartment is responsible for these more sustained increases is unknown.

Limitations: At the time of this study we did not have facilities for determining serum amiodarone levels. Comparison between the time courses of electrophysiologic changes and serum levels are ongoing in our laboratory.

The electrophysiologic data concern only the first 2 months of amiodarone therapy, and do not ascertain stable perpetuation of electrophysiologic influence during later maintenance therapy. Nevertheless, the 79% arrhythmia control rate is consistent with clinically meaningful maintenance of amiodarone effect during long-term therapy.

Our findings concerning VT inducibility should be interpreted in the context of the endpoints of our stimulation protocol, which included the induction of

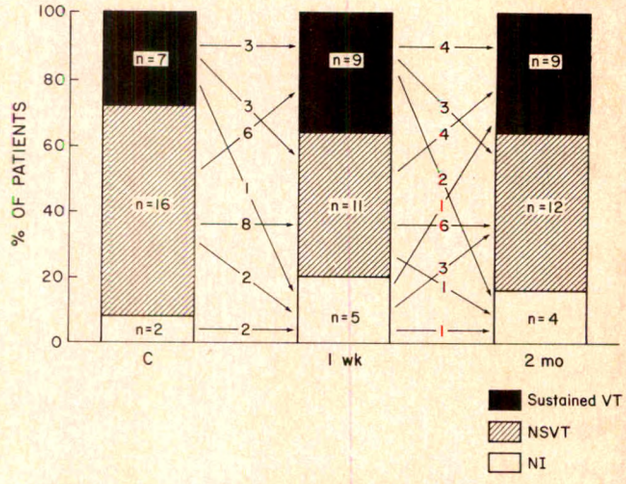

FIGURE 5. Proportion of patients with different inducible ventricular arrhythmias in the control state, after 1 week of amiodarone loading, and after 2 months of maintenance therapy. **Arrows** indicate the number of patients changing levels of inducibility or remaining at the same level of inducibility from 1 electrophysiologic study to the next. NI = no inducible ventricular tachycardia; NSVT = nonsustained ventricular tachycardia; VT = sustained ventricular tachycardia. See text for details.

at least 10 beats of rapid VT. For example, all of the patients with clinical sustained VT who are listed in Table II as having nonsustained VT inducible at control electrophysiologic study did have at least 10 beats of rapid VT, at which point the protocol was terminated. Higher incidences of inducible sustained VT might have resulted had we uniformly persisted until either a sustained arrhythmia or ventricular refractoriness was achieved.

The considerations used in this study to select maintenance dosing are somewhat complex in comparison to a uniform regimen. However, because of the differences in arrhythmia responsiveness and susceptibility to adverse effects, adherence to a fixed amiodarone dosing protocol may not be practical.[25] The clinical outcomes as well as the results of electrophysiologic testing at 2 months suggest that modification of a dosing protocol by electrophysiologic assessment after loading is a reasonable therapeutic alternative.

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Spontaneous Termination of Reciprocating Tachycardia Owing to Interaction of Dual Atrioventricular Nodal Pathways in Patients with an Accessory Pathway

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Retrospective analysis of the electrophysiologic recordings from 125 consecutive patients with reciprocating tachycardia involving an accessory atrioventricular (AV) pathway suggested, by the mode of spontaneous termination of reciprocating tachycardia, the coexistence of dual AV nodal pathways in 7 patients. Three different modes of spontaneous tachycardia termination were observed. In 2 patients with antidromic tachycardia, termination was a result of AV nodal reentry, preceded by a decrease in retrograde AV nodal conduction. In 3 other patients with antidromic tachycardia, termination occurred after a sudden switch from a slow to a fast AV nodal pathway, leading to conduction block in either the accessory pathway or the His-Purkinje system. In 2 patients with orthodromic tachycardia, termination was caused by a sudden change of anterograde conduction from a fast to a slow AV nodal pathway, eliciting an AV nodal echo beat. The interaction of dual AV nodal pathways within the reentry circuit incorporating the accessory pathway always inhibited sustained reciprocating tachycardia.

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The most frequent rhythm disorder in patients with the Wolff-Parkinson-White (WPW) syndrome is paroxysmal orthodromic reciprocating tachycardia, which involves the atrioventricular (AV) node in anterograde and the accessory AV pathway in retrograde direction.[1,2] Occasionally, supraventricular tachycardia may be an antidromic reciprocating tachycardia in which the impulse is conducted anterogradely over the accessory pathway and retrogradely over His bundle and AV node.[3]

In cases in which the AV nodal limb of the reentrant circuit consists of multiple conduction pathways, the arrhythmias may become more complex, and the interaction between these pathways and the single accessory AV connection may be important for the initiation and continuation of reentrant tachycardias.[4–6]

We report on the interaction of dual AV nodal pathways in the mechanism of spontaneous termination of reciprocating tachycardia in the WPW syndrome. Various modes of impulse conduction within the AV node during reciprocating tachycardia may lead to early cessation of tachycardia and may prevent sustained tachycardia in these patients.

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Methods

Patients: We retrospectively analyzed electrophysiologic studies of 125 consecutive patients with an accessory AV pathway to examine the mode of spontaneous termination of reciprocating tachycardia involving the accessory pathway. In 34 patients (27%) tachycardia terminated spontaneously: in the accessory pathway in 16, in the His-Purkinje system in 4, and by AV nodal involvement in 14 patients. Of these 14 patients, the electrophysiologic study suggested participation of dual AV nodal pathways in the mode of spontaneous tachycardia termination in 7. The records of these 7 patients form the basis of this report. All 7 patients had a history of palpitations. Episodes of nonsustained orthodromic tachycardia had been documented in 2 patients. There were 4 men and 3 women, mean age 38 years. Five patients had the typical electrocardiographic pattern of the WPW syndrome, whereas 2 patients had a normal surface electrocardiogram.

Electrophysiologic study: After patients gave informed, written consent, they were studied in the resting, nonsedated state. They had taken no medication for 48 hours. Using the Seldinger technique, quadripolar catheters were passed through both femoral veins and advanced to the high right atrium, coronary sinus and right ventricular apex. In patient 1 an additional quadripolar catheter was advanced into the left atrium through a patent foramen ovale. In all patients a bipolar catheter was positioned across the tricuspid valve to record His bundle electrograms. Our stimulation protocol has previously been reported.[7] All electrograms were recorded simultaneously on a 16-channel electrocardiograph at a paper speed of 100 mm/s. Stimulus strength was twice diastolic threshold and stimulus duration was 0.5 ms.

Definitions: Conventional definitions were used for refractory periods[8]; the presence of an accessory pathway was diagnosed by standard criteria,[9] as were antidromic or

TABLE I Electrophysiologic Data*

Pt	AP Location	A-ERP	A-FRP	AVN-ERP ant	AP-ERP ant	AP-ERP ret	VERP	Orthodromic CMT CL	Orthodromic CMT AH	Orthodromic CMT HV	Orthodromic CMT VA	Antidromic CMT CL	Antidromic CMT AV	Antidromic CMT VA	Max Duration of CMT
1	LL	240	270	—	<270	320	240					450	160	290	4 beats
2	LP	230	250	—	260	300	220					400	150	260	5 beats
3	LP	200	230	—	250	280	200					410	180	210	4 beats
4	LL	220	230	—	<230	190	180					320	110	220	7 beats
5	LL	220	250	—	<250	250	200					340	120	230	6 beats
6	LL	210	220	270† <A-FRP‡	CAP	220	210	320	130	35	80				6 sec
7	LP	220	230	290† <A-FRP‡	CAP	230	200	300	140	30	80				5 sec

* All values are in milliseconds.
† Fast atrioventricular nodal pathway.
‡ Slow atrioventricular nodal pathway.
A = atrium; AH = atrio-His conduction time; ant = anterograde; AP = accessory pathway; AV = atrioventricular conduction time; AVN = atrioventricular node; CAP = concealed accessory pathway; CL = cycle length; CMT = circus movement tachycardia; ERP = effective refractory period; FRP = functional refractory period; HV = His–ventricular conduction time; LL = left lateral; LP = left posterior; max = maximal; ret = retrograde; VA = ventriculoatrial conduction time.

orthodromic reciprocating tachycardia. The diagnosis of dual AV nodal pathways during basic pacing with the extrastimulus technique and of AV nodal echoes was made according to Denes et al[10] and Rosen et al.[11] A tachycardia was termed nonsustained when more than 3 beats were induced and its duration was less than 30 seconds. When the tachycardia lasted longer than 30 seconds it was termed sustained.

Drug intervention: To study the characteristics of retrograde conduction in patients 3, 4 and 5, with antidromic reciprocating tachycardia, 1 mg of atropine was administered intravenously before repetition of the stimulation protocol.

Patients were followed up for a mean of 11 months.

Results

Patients 1 to 5 had an accessory pathway capable of both anterograde and retrograde conduction, whereas patients 6 and 7 had a concealed accessory pathway.

Characteristics of tachycardia: Basic electrophysiologic data and characteristics of reciprocating tachycardia are summarized in Table I. Sustained tachycardia was not induced in any of our patients. After atropine, tachycardia became sustained in all 3 patients who received the drug.

Dual AV nodal pathways could not be diagnosed with the extrastimulus technique during basic atrial or ventricular pacing in patients 1 to 5, because the anterograde effective refractory period of the accessory pathway was shorter than the anterograde AV nodal refractory period, precluding disclosure of discontinuous AV nodal conduction curves. In patients 6 and 7, atrial pacing with the extrastimulus technique revealed discontinuous anterograde AV nodal conduction curves.

Modes of tachycardia termination: In all patients, the presence of dual AV nodal pathways was suggested by the mode of termination of reciprocating tachycardia. Three different modes of spontaneous termination were observed.

Atrioventricular nodal echo in antidromic tachycardia: Two patients (nos. 1 and 2) with antidromic reciprocating tachycardia revealed long retrograde conduction times (VA interval 290 and 250 ms, respectively) during tachycardia. In both patients exact measurements of retrograde AV nodal conduction time (HA interval) during tachycardia were not possible, since retrograde His potentials were obscured in the ventricular potentials of the His bundle area, with the exception of the tachycardia-initiating beat (Fig. 1). A sudden increase of retrograde conduction time during reciprocating tachycardia, measured by prolongation of the AA interval, led to the appearance of a His potential before onset of the last tachycardia beat. The QRS complex of this beat was narrower and had a different morphologic pattern than the previous tachycardia beats. Additionally, local activation time, measured with respect to the onset of the QRS complex, of proximal and distal right ventricle during the last tachycardia beat was shorter than that of the previous tachycardia beats.

These findings reflect that after a gradual increase in retrograde slow AV nodal pathway conduction, a fast AV nodal pathway becomes capable of anterograde conduction, leading to anterograde His bundle activation. Because of the simultaneous activation of the ventricle by this AV nodal echo beat and the wavefront coming across the accessory pathway, fusion occurs on the ventricular level. Tachycardia is terminated and sinus rhythm restored.

Change of atrioventricular nodal pathway during antidromic tachycardia: In the 3 other patients (nos. 3, 4 and 5) with antidromic reciprocating tachycardia, retrograde conduction time (VA interval) during tachycardia averaged 220 ms. Tachycardia termination was always preceded by a sudden shortening of retrograde conduction time, indicated by a decrease of the VA interval to an average of 140 ms. This sudden decrease of retrograde AV nodal conduction time led to termination of reciprocating tachycardia either on the atrial level (2 patients; Fig. 2) or, after anterograde conduction through the accessory pathway, on the ventricular level (1 patient). Bundle branch reentry beats were not induced in these patients during atrial or during ventricular pacing.

The assumed mechanism for this type of reciprocating tachycardia termination is a change of retrograde conduction from a slowly conducting to a rapidly conducting AV nodal pathway, leading to either antero-

grade block in the accessory pathway or retrograde block in the His-Purkinje-AV node axis.

Intravenous application of atropine invariably enhanced fast retrograde AV nodal pathway conduction, resulting in 1:1 ventriculoatrial conduction through the fast AV nodal pathway during sustained tachycardia in all 3 patients. Ventricular premature beats delivered during tachycardia neither advanced atrial activity nor changed retrograde atrial activation sequence.

Atrioventricular nodal echo in orthodromic tachycardia: In the 2 patients with orthodromic reciprocating tachycardia (nos. 6 and 7), termination occurred after a sudden change from short tachycardia cycles to a long cycle. Intracardiac recordings revealed that the increase of tachycardia cycle length was due to an increase of anterograde AV nodal conduction time (AH interval), followed by simultaneous activation of atria and ventricles (Fig. 3). Cycle length prolongation was accompanied by a change of retrograde atrial activation sequence. During tachycardia, earliest atrial activation occurred in the distal coronary sinus, followed by proximal coronary sinus, His area and high right atrium, suggesting conduction across a left laterally localized accessory pathway. After cycle length prolongation and termination of tachycardia, earliest activity occurred in the low right atrium, followed almost simultaneously by activation of coronary sinus and high right atrium. This activation sequence suggests retrograde conduction through the AV node.

The increase in anterograde AV nodal conduction time and the change in timing and sequence of retrograde atrial activation after an increase in tachycardia cycle length presumably reflects a switch of anterograde AV conduction from a fast to a slow AV nodal pathway. During reciprocating tachycardia anterograde conduction predominantly occurs through the fast AV nodal pathway and retrograde conduction through the accessory pathway. Sudden conduction block in the fast pathway switches anterograde conduction to the slow AV nodal pathway, allowing the impulse to reinvade the atria not only through the accessory pathway but also through the fast AV nodal pathway (AV nodal echo beat). It is postulated that simultaneous retrograde activation through the accessory pathway and the AV node leads to collision of both wavefronts on the atrial level, thereby terminating tachycardia and restoring sinus rhythm.

Follow-up: During a follow-up period of 11 ± 4 months, none of our patients received antiarrhythmic treatment, and sustained episodes of tachycardia were never documented.

Discussion

Spontaneous termination of reciprocating tachycardia in the presence of accessory AV pathways occurs

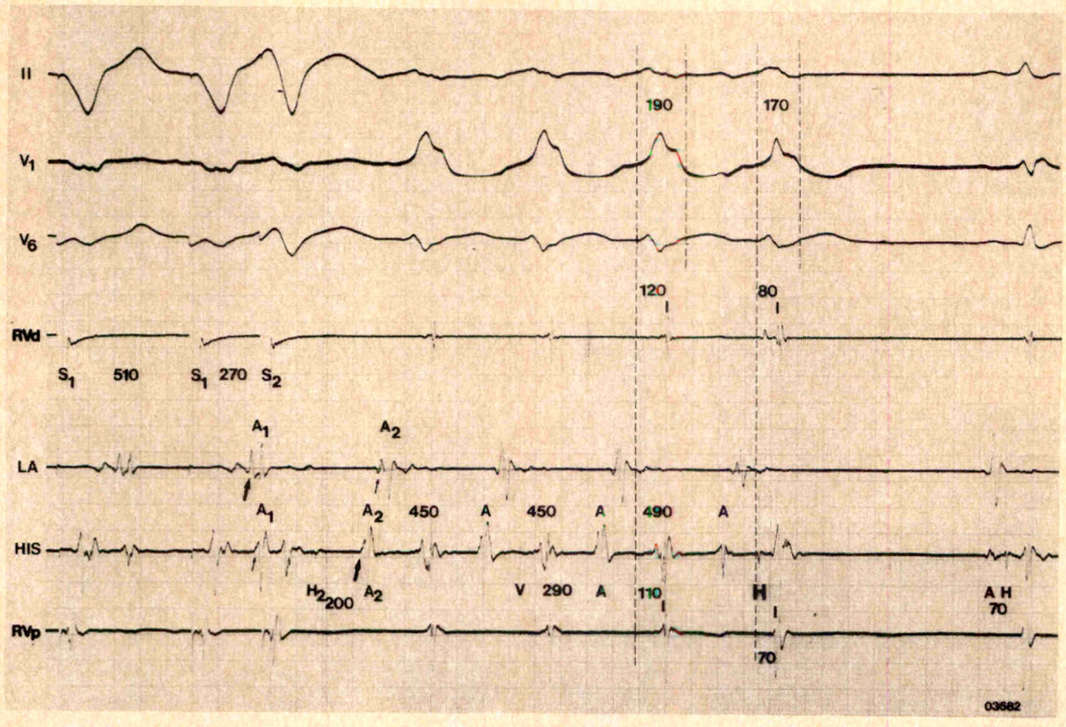

FIGURE 1. Patient 1. Delivery of a ventricular premature beat (S_2) after 270 ms during right ventricular pacing with a basic cycle length of 510 ms. **Arrows** mark retrograde atrial activation sequence (A_1), showing earliest activity during basic pacing (S_1S_1) in left atrium (LA) (**thick arrow**), followed by His bundle area (HIS, **thin arrow**), indicative of conduction through a left-sided accessory pathway. Following S_2, atrial activation (A_2) occurs after the appearence of a retrograde His potential (H_2A_2 200 ms). Earliest activation now occurs in HIS (**thick arrow**), followed by left atrium (**thin arrow**), indicative of conduction through the AV node. After conduction of A_2 to the ventricles, 4 tachycardia cycles with a wide QRS complex are initiated. Retrograde atrial activation sequence during tachycardia is the same as after S_2. After an increase in AA interval during tachycardia from 450 to 490 ms, a His potential (H) appears at the onset of the last tachycardia QRS complex. Note the difference in shape and width of this beat (170 ms), compared with the 3 previous beats (190 ms). Local activation times of distal (RVd) and proximal right ventricle (RVp), measured from the onsets of the QRS complexes (**dashed vertical lines**), shorten from 120 to 80 ms and from 110 to 70 ms, respectively. See text for explanation of the proposed mechanism.

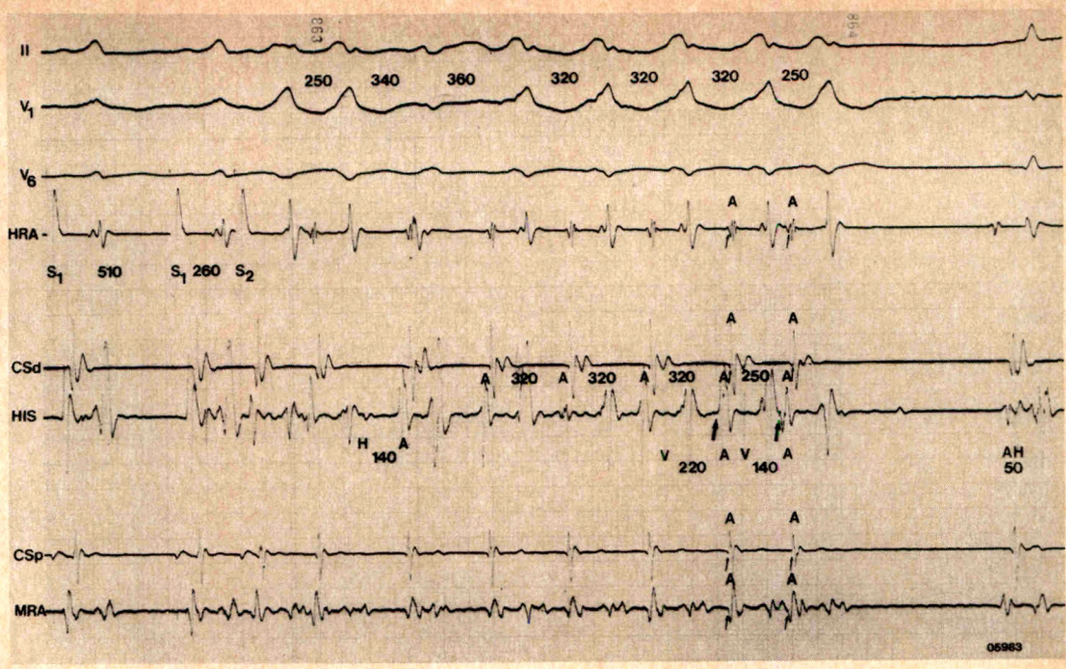

FIGURE 2. Patient 4. Delivery of a premature atrial beat (S_2) at 260 ms during right atrial pacing with a basic cycle length of 510 ms. S_2 initiates a tachycardia with a wide QRS complex. Retrograde atrial activation sequence during tachycardia revealed earliest activity in His bundle area (HIS) (**thick arrow**), followed by proximal coronary sinus (CSp), distal coronary sinus (CSd) and high right atrium (HRA) (**thin arrows**). After first tachycardia beat a retrograde His spike can be identified, suggesting retrograde conduction through the AV node. Note the spontaneous change of cycle length during tachycardia (250 to 360 ms) as a result of changes of VA interval. Tachycardia is antidromic. Sudden shortening of VA interval from 220 to 140 ms does not change retrograde atrial activation sequence (**arrows on right**) and anterograde conduction through the accessory pathway, but leads to retrograde block. See text for proposed mechanism. MRA = midright atrium.

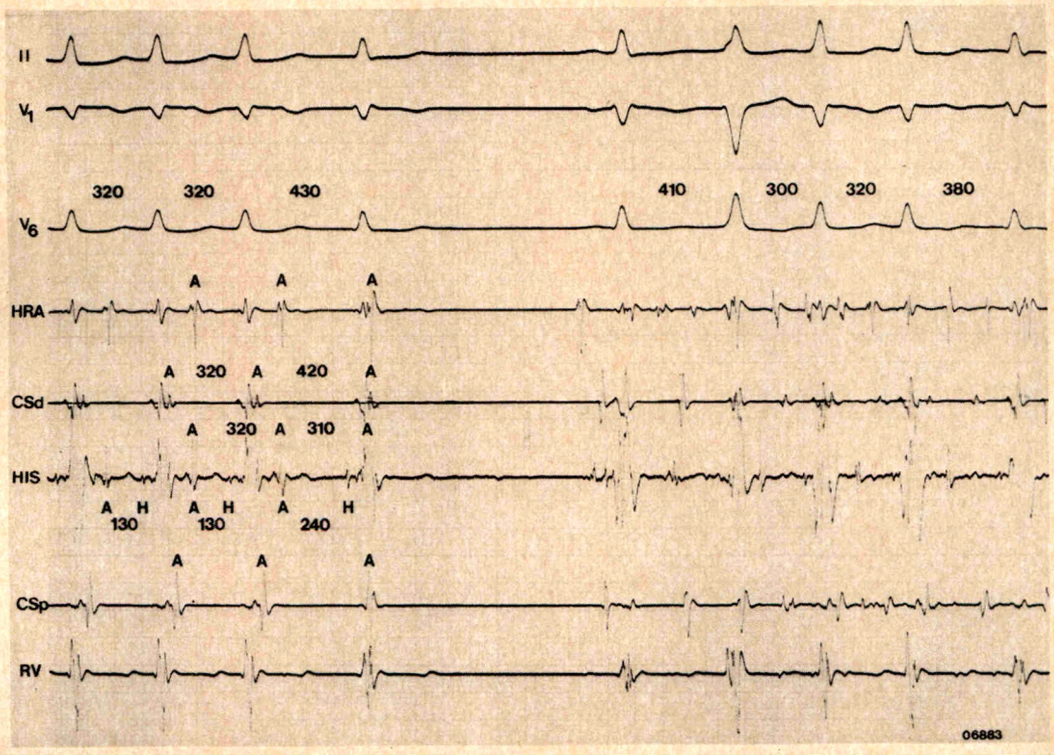

FIGURE 3. Patient 6. Spontaneous termination of orthodromic reciprocating tachycardia (cycle length 320 ms) after a sudden increase of cycle length to 430 ms. This cycle length prolongation is caused by an increase in the AH interval from 130 to 240 ms. Retrograde atrial activation sequence during tachycardia shows earliest activity in distal coronary sinus (CSd), followed by proximal coronary sinus (CSp), His bundle area (HIS) and high right atrium (HRA). After cycle length prolongation, earliest retrograde activation is observed in HIS, followed almost simultaneously by CSp, CSd and HRA. Note altered QRS morphologic pattern (s in II, r′ in V_1) in surface leads II and V_1 as a result of altered retrograde atrial activation. After termination of tachycardia, impure atrial flutter is spontaneously initiated. See text for proposed mechanism. RV = right ventricle.

in about 40% of patients undergoing electrophysiologic study.[12] Usually, the site of block is the accessory pathway or the AV node, but occasionally it is the His-Purkinje system. Several investigators have suggested the coexistence of dual AV nodal pathways and anomalous AV bypass tracts in patients. The electrophysiologic importance of this phenomenon was mainly seen in the coexistence of both AV nodal and AV reentrant tachycardia,[13,14] and in the inducibility and maintenance of these types of tachycardia.[5,6] The electrophysiologic demonstration of dual AV nodal pathways in the presence of an accessory AV connection included alternation of tachycardia cycle length and the recording of discontinuous AV nodal conduction curves.[4,5,15]

In this study we have shown that the presence of dual AV nodal pathways in patients with an accessory AV pathway may be diagnosed only indirectly, by the mode of spontaneous termination of reciprocating tachycardia. Although different modes of tachycardia termination were observed, the underlying mechanism was always a sudden switch between a slowly conducting and a rapidly conducting AV nodal pathway, either concomitant with intranodal reentry or not. It is not known why intranodal conduction changes from one pathway to another during reciprocating tachycardia. Changes of refractoriness after the onset of and during tachycardia or a fatigue phenomenon in one pathway may be the cause.

Instead of intranodal reentry, termination of tachycardia might also be caused by His extrasystoles. However, this mechanism appears to be unlikely because, in each patient, the time intervals leading to termination were identical in all episodes of tachycardia.

The possibility of a second accessory pathway responsible for the change in retrograde conduction during tachycardia must be considered. Exclusion of such a pathway is only possible by indirect criteria. After retrograde block had occurred in the proved accessory pathway, retrograde conduction to the atria was in all patients dependent on the S_1H_2 interval, never on the S_1S_2 (or V_1V_2) interval. The S_1H_2 (and consequently A_1A_2) intervals progressively prolonged with gradual shortening of S_1S_2. Retrograde atrial activation was always preceded by a His deflection before the onset of tachycardia. Furthermore, the retrograde atrial activation sequence was always in accordance with conduction through the AV node and it never changed, neither after the first tachycardia activation sequence nor during the following tachycardia beats. In 3 patients with sustained tachycardia after administration of atropine, delivery of ventricular premature beats during tachycardia never advanced atrial activity or changed retrograde atrial activation sequence. Finally, it appears highly unlikely that all patients had a second concealed accessory pathway which would have to be located septally with decremental conduction properties.

In 3 patients without an echo phenomenon, the lack of retrograde His potentials during antidromic tachycardia did not allow us to determine the mechanism of the sudden decrease of retrograde conduction time. Retrograde input into the AV node through different parts of the bundle branch system may cause cycle length variations in antidromic reciprocating tachycardia.[16] However, in our patients, no form of bundle branch reentry could be induced, neither during atrial nor during ventricular stimulation; moreover, atropine, which is known to have a greater influence on nodal than on subnodal tissue, changed the characteristics of the induced arrhythmia.[17]

The high percentage of antidromic reciprocating tachycardia found in our patients is unusual. We do not know whether patients with antidromic reciprocating tachycardia have electrophysiologically functioning dual AV nodal pathways more often than patients with orthodromic reciprocating tachycardia or whether the anterograde or retrograde conduction characteristics of the AV node are different in these patients.

The early spontaneous termination of reciprocating tachycardia in patients with an accessory pathway owing to interaction of dual AV nodal pathways, as proposed in this study, may indicate that these patients have clinically less symptomatic arrhythmias than patients without dual AV nodal pathways.

Acknowledgment: We are indebted to Monika Hoch for technical assistance.

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Electrophysiologic Evaluation of the Antiarrhythmic Effects of N-Acetylprocainamide for Ventricular Tachycardia Secondary to Coronary Artery Disease

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Antiarrhythmic properties of N-acetylprocainamide (NAPA), an active metabolite of procainamide, were studied in 12 patients with coronary artery disease who presented with cardiac arrest or documented sustained ventricular tachycardia (VT). Programmed electrical stimulation (PES) studies were performed in 10 men and 2 women, aged 52 to 80 years (mean 63), who had a left ventricular ejection fraction of 16 to 69% (mean 33). All patients tested had inducible VT provoked by PES without antiarrhythmic therapy. Patients were then tested with procainamide, 1,000 mg administered intravenously. VT could be provoked after procainamide treatment in 8 of 10 patients. Twenty-four to 36 hours later NAPA was administered, 18 mg/kg body weight intravenously, and PES was performed after 20 minutes. NAPA did not significantly change heart rate, mean arterial blood pressure, electrocardiographic intervals and AH or HV conduction times. The QT interval lengthened, but not significantly. The mean serum NAPA levels were 15.7 ± 4 μg/ml in the group protected by NAPA and 16.2 ± 4 μg/ml in the group not protected by NAPA. Five patients were discharged with NAPA therapy, 1.5 g orally every 8 hours. Two patients have been maintained with chronic NAPA therapy (10 ± 3 months), and 2 patients had breakthrough VT on follow-up Holter monitoring and alternative therapy was given. One patient died while taking oral therapy. NAPA demonstrates antiarrhythmic efficacy in preventing induction of VT by PES in a high-risk group of patients. During chronic oral therapy in some patients, NAPA appears to be well tolerated, with antiarrhythmic efficacy that may be enhanced with further upward dose titration.

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N-acetylprocainamide (NAPA), the N-acetylated metabolite of procainamide, has been shown to have antiarrhythmic properties in humans and in isolated tissue preparations.[1–4] Some studies reported that NAPA has antiarrhythmic properties similar to those of procainamide.[5–7] However, the electrophysiologic properties of NAPA in isolated Purkinje fiber preparations are different from those of its parent compound, procainamide, in that it neither suppresses automaticity because of phase 4 depolarization nor depresses action potential amplitude or maximal upstroke velocity.[8] NAPA apparently exerts its antiarrhythmic effects through prolongation of the action potential duration and the effective refractory period.[9,10] NAPA has an advantage over the parent compound by having a longer elimination half-life of approximately 10 hours,[11] and a substantially lower incidence of the drug-induced lupus-like syndrome.[12,13] Earlier clinical studies described antiarrhythmic properties of NAPA during chronic oral dosing in humans,[14–18] but did not deal with its efficacy in the electrophysiology laboratory during acute intravenous administration and programmed electrical stimulation (PES).

To determine the effectiveness of NAPA in preventing induction of ventricular tachycardia (VT) by PES, we studied patients who presented with cardiac arrest or a history of sustained VT. If NAPA was found to be effective at PES testing, patients were treated with NAPA to assess its efficacy during long-term therapy.

Methods

Twelve patients (10 men, 2 women) with a history of cardiac arrest and 2 with sustained VT were evaluated using electrophysiologic methods to determine antiarrhythmic therapy. All antiarrhythmic drugs, calcium antagonists and β blockers were discontinued for 5 half-lives before the initiation of the study. Therapy with nitrates and diuretic drugs was continued for the treatment of angina and symptoms of congestive heart

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TABLE I Characteristics of the Patient Group with Coronary Artery Disease

Pt	Age (yr)	EF (%)	NYHA Class	Presenting Arrhythmia
L.S.	53	15	IV	CA
W.A.	72	. . .	III	CA
C.V.	62	28	III	CA
R.S.	57	43	II	VT
S.A.	65	20	IV	CA
D.S.	66	69	II	CA
L.P.	80	. . .	I	CA
J.B.	58	50	II	CA
L.D.	78	40	III	VT
L.V.	52	42	II	CA
J.C.	64	16	III	CA
L.C.	65	20	III	CA

CA = cardiac arrest; EF = ejection fraction; NYHA = New York Heart Association; VT = sustained ventricular tachycardia (>30 sec); . . . = technically inadequate study.

failure. Baseline electrocardiogram, chest x-ray, urinalysis, and hematologic and chemistry profiles were also obtained. Informed consent was obtained before each study. The consent form and protocol were approved by the Committee on Clinical Investigation at the Albert Einstein College of Medicine.

Drug infusion protocol: Baseline heart rate, blood pressure, PR interval, QRS, QT duration, sinus node recovery times, atrial-His and His-ventricular conduction times were recorded. The patients then received an intravenous infusion of NAPA at a dose of 18 mg/kg body weight over 20 minutes. Electrophysiologic evaluations were done at the end of 20 minutes of the infusion. All baseline variables were repeated and the patients then underwent serial drug testing with the PES protocol as outlined later.

During all PES studies, before and after drug administration, surface electrocardiographic leads I, II, aVF and V_5 were continuously monitored and printed on 8-channel paper using a Siemens Elema mingograph.

Chronic drug therapy: The patients who were protected with NAPA were then given oral therapy, 1.5 g every 8 hours. They were then followed up every month with monitoring of NAPA serum levels, hematologic and chemistry profiles, electrocardiography, urinalysis and Holter electrocardiographic monitoring.

Programmed electrical stimulation protocol: After the patients gave informed consent, PES was performed using a hexapolar catheter introduced transvenously in the apex of the right ventricle. For patients in whom VT could not be induced from the right ventricular apex, the catheter was repositioned in the right ventricular outflow tract. A digital stimulator (Bloom Associates) was used to deliver rectangular electrical impulses 2 ms in duration with amplitude set at twice diastolic threshold. The right ventricle was driven with a pacing train of 6 beats at a cycle length of 500 ms with an intertrain interval of 8 seconds.

Single premature ventricular stimuli (S_2) were introduced in late electrical diastole, starting at 500 ms from the end of the pacing train and progressively introduced earlier by 10 ms decrements. The shortest interval at which S_2 failed to evoke a depolarization was termed the effective refractory period. The stimulus was brought out 10 ms further from the first stimulus refractory period, and a second extra stimulus was introduced at 500 ms from this last stimulus. This programmed introduction of premature stimulus was performed until VT (more than 10 beats) was obtained or until 3 premature stimuli were introduced.

Nonsustained VT was defined as VT of more than 10 beats terminating spontaneously, and sustained VT was defined as VT lasting 30 seconds or requiring either pacing techniques or cardioversion to terminate the tachycardia. Patients who had VT provoked by 3 stimuli while not taking antiarrhythmic agents were evaluated by 4 stimuli while taking antiarrhythmic therapy. To be protected by a drug, 4 stimuli could not provoke VT in these patients.

Serum N-acetylprocainamide determination: Analysis of serum NAPA levels were performed by an independent drug laboratory at the clinical pharmacology section of the Northwestern University School of Medicine using a high-pressure liquid gas chromatographic technique with a sensitivity of 1 μg/ml.

Statistical analysis: Data are expressed as mean ± standard error of the mean. Differences between the means were determined by the Student t test and for multiple comparisons, an analysis of variance was used. A 2-tailed test was used to determine the level of significance. The JT interval was calculated as the QT interval minus the QRS duration. The percent change of the JT interval and the effective refractory period of the first extrastimulus (S_2) were compared using linear regression and a Z transform to determine significance.

Results

The study population consisted of 12 patients (10 men, 2 women) average age 63 ± 2 years (Table I). The presenting problem was a cardiac arrest in 10 patients (83%) and sustained VT in 2 (17%). Before electrophysiologic evaluation, the patients had poor clinical results with an average of 2 drugs (breakthrough VT or development of toxic side effects). The mean left ventricular ejection fraction for the patient group was 33 ± 6%. At the time electrophysiologic studies were performed, 1 patient was in New York Heart Association functional class I, 5 were in class II, 4 were in class III and 2 were in class IV.

Electrophysiologic studies: The PES studies were performed in patients whose antiarrhythmic medications were discontinued for at least 5 half-lives. All patients who were entered into the study had inducible VT by PES techniques (Fig. 1). Eight patients (67%) had nonsustained VT induced (12 to 30 seconds of VT), and 4 patients (33%) had sustained VT induced, which was terminated with direct current countershock in 2 patients (17%) and pacing techniques in 2 (17%). The mean rate of VT during the control run was 278 ± 9 beat/min. If nonsustained VT developed, we did not continue to provoke sustained VT but accepted the nonsustained VT as an index of electrical instability and proceeded to acute antiarrhythmic drug testing.

Results of drug testing: After intravenous infusion of NAPA, mean arterial blood pressure, heart rate, PR interval, QRS duration, QTc, AH and HV intervals did not change significantly. After NAPA was given, VT was no longer inducible in 5 patients (42%). VT was induced in 7 patients (58%) at a slower mean rate of 220 beats/min ($p < 0.05$) after administration of NAPA. The effective refractory period was prolonged significantly for the first extrastimulus, from 238 ± 5 to 291 ± 13 ms ($p < 0.01$). The mean serum NAPA level in the "protected" group was 15.7 ± 4 μg/ml and the mean NAPA level in the patients with inducible VT was 16.2 ± 4 μg/ml. Five of the 7 patients (71%) who were not protected at PES with NAPA required experimental agents to control their VT. The patients who were not protected by

TABLE II Effects of Intravenous N-Acetylprocainamide (NAPA) on Electrocardiographic Intervals and Ventricular Refractoriness in Relation to the Effects of the Drug on the Inducibility of Ventricular Tachycardia

	HR (beats/min)	PR (ms)	QRS (ms)	QTc (m)	ERP S_2* (ms)	ERP S_3† (ms)
Control	79 ± 5	179 ± 8	94 ± 8	429 ± 15	235 ± 5	197 ± 4
NAPA (18 mg/kg i.v.)						
Protected	84 ± 7	170 ± 9	108 ± 20	460 ± 22	298 ± 13‡	273 ± 21‡
Inducible	77 ± 5	188 ± 9	103 ± 9	467 ± 10	277 ± 10‡	278 ± 52‡

* ERP S_2 = effective refractory period of the first extra stimulus.
† ERP S_3 = effective refractory period of the second extra stimulus.
‡ ERP significantly different from control values ($p < 0.05$).
HR = heart rate.

NAPA were discharged taking the following agents: lorcainide (1 patient), amiodarone (2 patients) and quinidine, ethmozine, pirmenol and procainamide (1 patient each).

Three additional patients with a history of cardiac arrest and a cardiomyopathy without CAD were studied. All 3 had VT provokable without antiarrhythmic therapy; 1 was protected with NAPA, and is alive and well after 10 months of oral therapy.

The clinical electrophysiologic profile of NAPA did not show a prolongation in conduction as measured by the HV interval or the QRS duration (Table II). The ventricular refractory period was measured by the extrastimulus technique and repolarization was determined by measurement of the JT interval. The mean JT increased from 266 ± 12 to 297 ± 10 ms ($p < 0.05$). To determine the relative effects of NAPA on refractoriness and repolarization, the percent change from the drug-free state in refractoriness was plotted on the ordinate and the percent change in the JT interval plotted on the abscissa (Fig. 2). This relation was examined in patients that were protected at PES studies and those not protected by NAPA. A linear relation was found ($r = 0.95$) for the group in which NAPA prevented VT induction but not for the group in which NAPA had no effect on VT inducibility ($r = -0.26$). The 2 groups were significantly different ($p < 0.005$).

Procainamide and N-acetylprocainamide comparative results: Ten patients were tested in the electrophysiology laboratory with procainamide and NAPA. The other 3 patients had poor clinical results with procainamide; 2 had breakthrough VT and 1 patient showed toxic side effects. Eight of the 10 patients who were tested with procainamide had inducible VT at PES. The 2 patients found to be protected with procainamide had inducible VT with NAPA (Fig. 1).

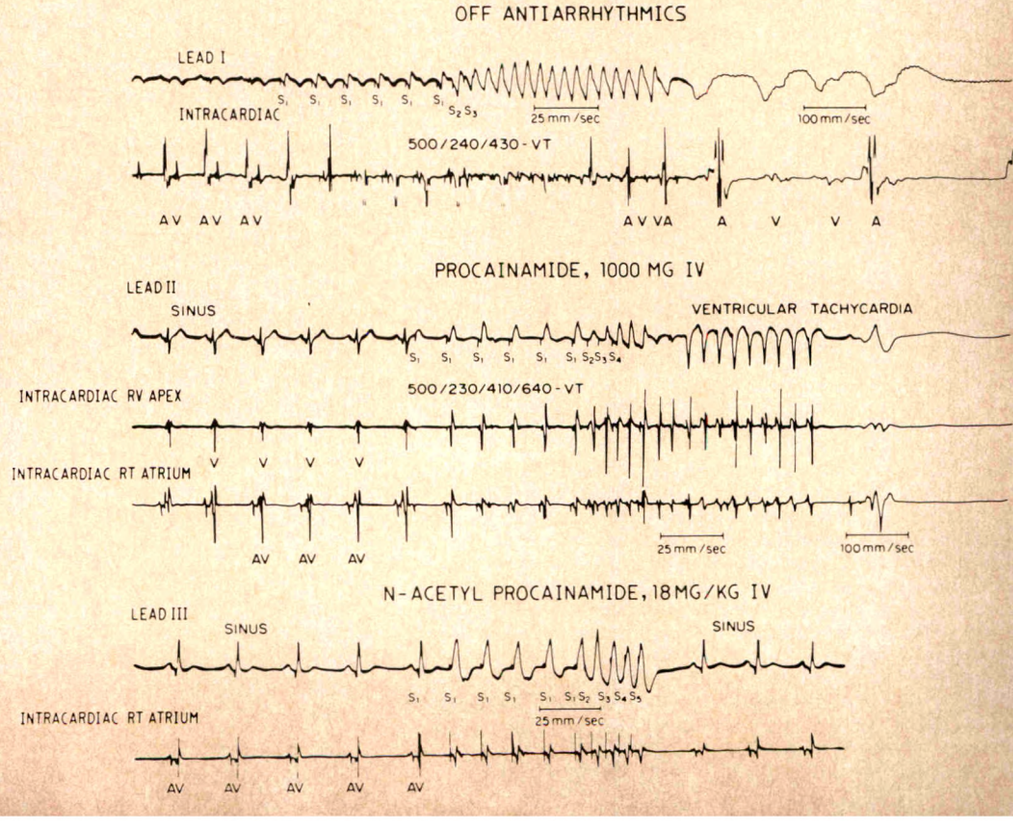

FIGURE 1. Differential effects of N-acetylprocainamide and procainamide on electrophysiologic testing. Electrophysiologic studies were initially performed without antiarrhythmic therapy with induction of ventricular tachycardia (VT) (**top**) followed by acute drug testing. Procainamide (1,000 mg administered intravenously (IV)) failed to prevent induction of VT (**middle**). After 30 hours of drug washout, N-acetylprocainamide was administered intravenously (18 mg/kg) and VT could not be induced at electrophysiologic testing (**bottom**) despite the introduction of 4 premature stimuli.

TABLE III Serum Concentrations of N-Acetylprocainamide (NAPA) and Procainamide Relative to Their Effects on Induction of Ventricular Tachycardia and During Chronic Therapy with NAPA

Pt	Procainamide at PES* (μg/ml)	NAPA at PES (18 mg/kg)	NAPA (1.5 g tid) Chronic Therapy
	Patients Protected		
R.S.	0.10	14 (μg/ml)	37 (μg/ml)
W.A.	0.17	19	38
S.A.	0.40	16	Deceased
C.V.	0.20	17	12†
L.S.	0.15	8	11†
	Patients with Inducible Ventricular Tachycardia		
L.C.	0.5	18	
J.B.	<1	18	
J.C.	ND	20	
E.H.	ND	19	
R.K.	0.2	11	
L.P.	ND	18	
D.S.	ND	15	

* Concentration of procainamide when only NAPA was given (measurement of deacytalation).
† Patients with breakthrough arrhythmias.
ND = not detectable; PES = programmed electrical stimulation; tid = 3 times daily.

The mean procainamide level in the group protected with procainamide was 7.7 ± 1 μg/ml and the level in the nonprotected group was 9.2 ± 3 μg/ml (Table III). Six patients were protected with NAPA and 3 were tested with procainamide; in all 3, VT could be induced using PES techniques. There was no correlation between effective refractory period and JT interval for either the protected, nonprotected or combined groups receiving procainamide.

Long-term experience: Five patients (with coronary artery disease) were discharged from the hospital receiving oral NAPA. Three patients are doing well, with no VT on Holter monitoring, after 10 ± 3 months of follow-up. These patients have a mean NAPA level of 32 ± 12 μg/ml. One of 5 patients was discharged from the hospital by his primary physician before NAPA serum levels could be determined. The patient died 2 days later. The cause of death and compliance with the oral NAPA protocol remain unknown. Two of the remaining 5 patients who were taking NAPA had breakthrough nonsustained VT on Holter monitoring, NAPA therapy was discontinued. Antiarrhythmic efficacy may have been enhanced with further upward dose titration. The adverse effects with NAPA therapy were minor and included nausea and dizziness. These effects have diminished with continuation of drug therapy.

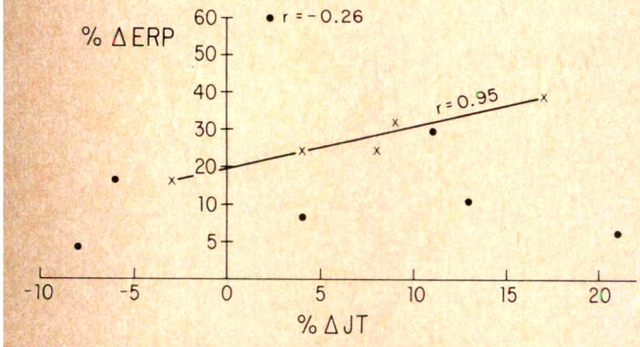

FIGURE 2. The correlation between changes in the JT interval (% ΔJT) and those in the effective refractory period (% ΔERP) relative to the effects of intravenous N-acetylprocainamide (NAPA) on the inducibility of ventricular tachycardia in patients with life-threatening ventricular tachyarrhythmias: The percent change in the JT interval after NAPA administration is calculated for each patient and plotted on the **abscissa** while the percent change in the effective refractory period (ERP S_2) after NAPA is plotted on the **ordinate.** In the group protected by NAPA (x—x), a linear correlation is seen between changes in JT and ERP (r = 0.95), whereas in the group in which ventricular tachycardia could still be induced (●), no correlation was seen between the changes in ERP and JT (r = −0.26). The relation of ERP and JT in the protected group are significantly different from that in the group in whom ventricular tachycardia could still be provoked ($p < 0.005$) after NAPA administration.

Discussion

PES techniques in our laboratory found NAPA to be an effective antiarrhythmic agent in a drug-resistant group. This group was at high risk of sudden death owing to ventricular tachyarrhythmias in the setting of impaired ventricular function; only 2 of the 12 had responded to procainamide therapy. Thus, this group could be considered a drug-resistant population, and the 40% efficacy of intravenous NAPA is impressive.

NAPA appeared to have an effect on the measured clinical electrophysiologic variables as might be expected from the results of cellular electrophysiologic studies.[8–10] Unlike the membrane-active "quinidine-like" or class Ia agents, NAPA did not prolong the QRS duration or the His-Purkinje conduction time as measured by the HV interval. NAPA did, however significantly prolong the JT interval, a measure of repolarization and voltage-dependent myocardial refractoriness determined by the extrastimulus technique. A comparison of the change in JT interval and effective refractory period S_2 showed a linear correlation for the protected group, but not for the nonprotected group. This correlation of JT interval and effective refractory period may represent an insight into the antiarrhythmic mechanism of NAPA and, possibly, other type III agents. In fact, studies in humans and dogs with bepridil, a calcium-blocking agent that prolongs the QT

interval, showed a similar relation, whereas quinidine failed to show this type of relation.[19,20] Prolonging repolarization may increase myocardial electrical homogeneity so that a stimulus causing focal reexcitation falls on a myocardium uniformly still refractory to stimulation. The heterogeneity of myocardial refractoriness caused by ischemic heart disease or myopathy may set the stage for a reentrant tachycardia. A nonuniform prolongation in repolarization may favor the development of ventricular tachyarrhythmias.[21] Uniform prolongation of repolarization would prolong refractoriness and may thus prevent reentrant tachycardias. The current study suggests that when refractoriness and repolarization are effected in concert, NAPA is effective in preventing VT induction.

Our results with chronic oral therapy show the need for oral dose titration. In 1 patient, (who died suddenly and had been in New York Heart Association functional class IV), we could not provide predischarge counseling with respect to drug dosage or determine the adequacy of therapeutic NAPA levels. The 2 other patients with nonsustained VT on Holter monitoring, in retrospect, had NAPA levels that may have permitted higher drug dosages to be administered. One patient with VT had an NAPA level during chronic therapy slightly lower than that after intravenous drug administration, preventing VT induction; the other patient with breakthrough VT had a NAPA level slightly higher than that found at the PES study. Whether a direct relation exists between the effects of intravenous NAPA preventing VT induction and long-term clinical outcome with chronic drug therapy, could not be established in the present study because of the limited study population. The results do suggest promise and indicate the need for further study using higher oral NAPA doses with correspondingly higher chronic serum concentrations.

Atkinson et al[17] found that oral NAPA causes a significant reduction in frequency of ventricular premature complexes (VPCs) in 9 of 10 patients, with 1 patient showing an increase in frequency of ectopic rhythm. Long-term follow-up of these patients shows a 70% reduction in mean VPC frequency. Also, when the NAPA levels were subtherapeutic, there was an increase in VPC frequency. Kluger et al[14,16] found that NAPA was effective, with acute intravenous administration causing a 70% reduction in VPCs. However, over a 12-month period, 8 of 20 patients withdrew from the study because of recurrent arrhythmias or death. Only 6 of the initial 29 patients had a persistent 70% reduction in VPC frequency. NAPA levels were not reported in the chronic phase of this study, and it is not clear if the patients with breakthrough arrhythmias had subtherapeutic or elevated levels of NAPA. Winkle et al[15] studied 11 patients receiving oral therapy and found that only 2 could achieve a 90% reduction in VPC frequency with NAPA. Lowering the criteria of drug efficacy to a 70% reduction in VPC frequency did not alter these findings. Our data in patients with life-threatening arrhythmias suggest that NAPA is effective in preventing VT induction at acute drug testing and may prevent spontaneous arrhythmias in selected patients.

NAPA has several potential advantages over procainamide in terms of adverse effects. Unlike the parent compound, procainamide, NAPA is not prone to induce the lupus syndrome or other immunologically mediated adverse effects.[20] In addition, NAPA has been reported to either augment contractility[23] or to have no significant depressant effect on cardiac function in patients undergoing diagnostic catheterization for ischemic heart disease (Josephson MA and Singh BN, personal communication). This finding is in contrast to the negative inotropic action of most antiarrhythmic agents.

NAPA appears to possess a low adverse reaction profile and to be effective in preventing VT induction at acute drug testing using PES techniques. Chronic oral administration of NAPA must be followed with serum level determinations and Holter monitoring. Increased oral dosing may be indicated because the effective chronic NAPA levels appear to be higher than previously believed and better tolerated.

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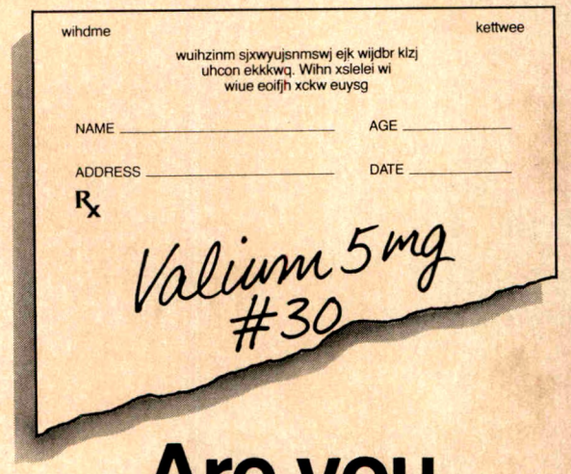

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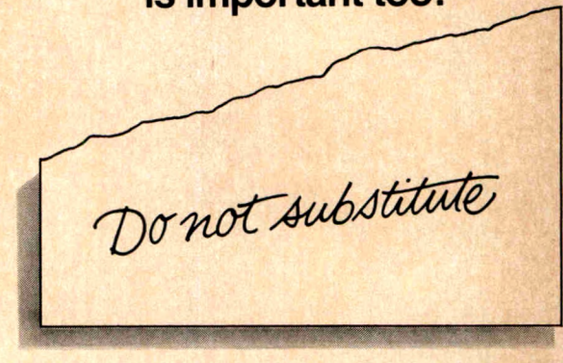

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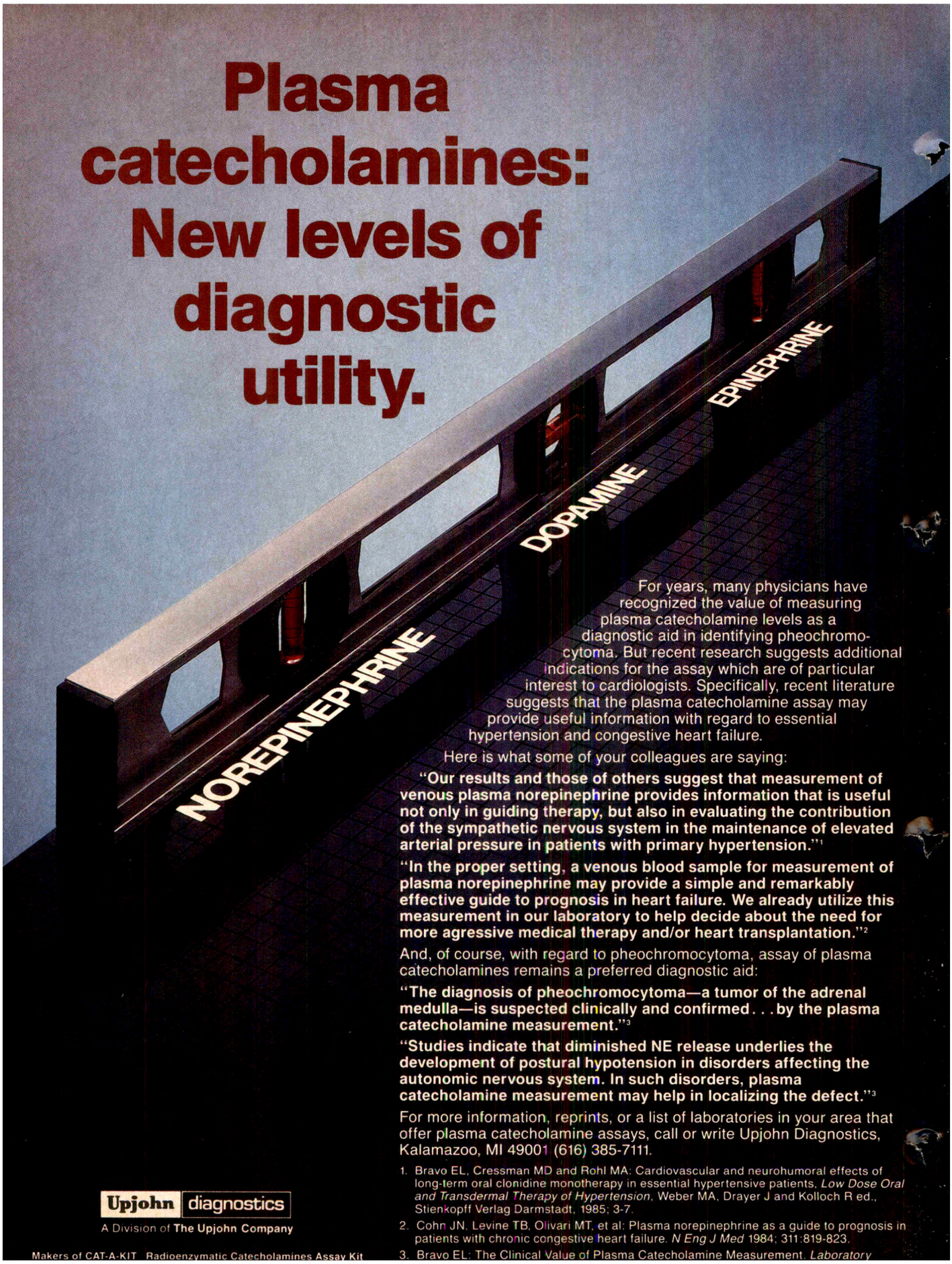

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Electropharmacologic Testing in Sustained Ventricular Tachycardia Associated with Coronary Heart Disease: Value of the Response to Intravenous Procainamide in Predicting the Response to Oral Procainamide and Oral Quinidine Treatment

DANIEL S. OSERAN, MD, ELI S. GANG, MD, MARK E. ROSENTHAL, MD, WILLIAM J. MANDEL, MD, and THOMAS PETER, MD

Twenty patients with inducible, sustained ventricular tachycardia (VT) were prospectively evaluated to determine whether the response to intravenous procainamide administration, as assessed by programmed ventricular stimulation, predicted the response to oral procainamide and oral quinidine treatment. Six patients (30%) responded to intravenous procainamide (fewer than 10 beats of inducible VT). Ten of 20 patients (50%) responded to oral quinidine and 5 (25%) responded to oral procainamide. Mean drug serum levels were 11.3 ± 2.1 μg/ml for intravenous procainamide, 5.4 ± 0.8 μg/ml for oral quinidine and 11.7 ± 3.4 μg/ml for oral procainamide. There was no significant difference in serum levels between those who responded and those who did not. Fifteen patients (75%) had a concordant drug response for intravenous and oral procainamide. Ten patients (50%) had a concordant response for intravenous procainamide and oral quinidine. Fifteen patients (75%) had a concordant drug response for oral procainamide and oral quinidine. Thus, in patients with sustained VT, the response to intravenous procainamide does not reliably predict the response to oral quinidine or oral procainamide, and serial day drug testing with these agents is necessary. Furthermore, high-dose quinidine therapy may be more effective in controlling VT in these patients than procainamide.

(Am J Cardiol 1985;56:883–886)

Serial electrophysiologic testing has been proposed as a means of selecting effective antiarrhythmic drug therapy in patients with ventricular tachycardia (VT).[1–4] This approach is based on the premise that the acute or subacute response to antiarrhythmic agents, as assessed by programmed ventricular stimulation, is predictive of the long-term clinical response to that agent. Some investigators suggest that the response to intravenous procainamide at the time of initial testing is predictive of the response to other antiarrhythmic agents.[5–7] The purpose of this study was to determine, in a prospective fashion, if the response to intravenous procainamide at the time of electrophysiologic study predicted the subsequent response to oral procainamide and oral quinidine in patients with sustained VT.

From the Department of Medicine, Division of Cardiology, Cedars-Sinai Medical Center, Los Angeles, California. Manuscript received February 5, 1985; revised manuscript received May 24, 1985, accepted May 28, 1985.

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Methods

Patients: The study group consisted of 20 patients (17 men, 3 women), aged 30 to 77 years. All 20 patients had coronary heart disease.

All patients had inducible sustained VT at the time of electrophysiologic study. The referring diagnosis was recurrent sustained VT in 7 patients, sudden cardiac death in 7, and unexplained syncope in 6. Patients with a history of an adverse reaction to procainamide or quinidine were excluded. Three other patients could not complete the study because of side effects from quinidine treatment.

Electrophysiologic study protocol: Studies were performed in the postabsorptive state after the patient gave informed consent. All antiarrhythmic agents had been stopped for at least 5 half-lives before testing. Electrode catheters were inserted percutaneously and were positioned under fluoroscopic guidance in the high right atrium, right ventricular apex and His bundle position. Intracardiac recordings were filtered at 30 to 500 Hz and displayed simultaneously with 3 surface electrocardiographic leads (I, aVF and V_1) on a multichannel oscilloscope (Electronics for Medicine, VR-12). Stimulation was performed using a programmable stimulator (Bloom Associates) that delivered rectangular impulses 2 ms in duration. Programmed ventricular stimulation included the introduction of 1, 2 and 3 ventricular extrastimuli from

TABLE I Results of Programmed Ventricular Stimulation

	Intravenous Procainamide			Oral Procainamide			Oral Quinidine	
Pt	PA (μg/ml)	NAPA (μg/ml)	Response to PVS (no. of beats)	PA (μg/ml)	NAPA (μg/ml)	Response to PVS (no. of beats)	Q (μg/ml)	Response to PVS (no. of beats)
1	9.8	1.5	VT-S	7.3	5.4	VT-S	4.2	VT-S
2	9.9	1.0	VT-S	10.9	5.7	VT-S	4.9	VT-S
3	8.7	2.2	NI	9.7	6.3	NI	4.9	NI
4	13.2	1.8	VT-NS (20)	15.2	11.1	VT-S	6.6	VT-S
5	13.7	1.6	VT-S	9.6	9.5	VT-S	7.5	VT-S
6	9.2	1.6	VT-S	15.2	8.2	VT-NS (8)	4.9	NI
7	10.8	1.9	VT-S	13.0	4.1	VT-S	6.1	VT-S
8	10.5	1.1	NI	9.1	4.1	NI	5.4	NI
9	11.0	1.1	VT-NS (11)	11.0	4.6	NI	4.7	NI
10	13.5	1.2	VT-S	7.7	10.3	VT-S	5.8	NI
11	16.3	1.4	VT-S	7.6	8.5	VT-NS (21)	5.1	VT-S
12	8.7	1.1	VT-S	20.4	6.2	VT-S	5.0	VT-S
13	9.3	1.2	NI	17.6	7.6	NI	4.5	NI
14	10.7	1.9	VT-NS (17)	11.5	14.5	VT-NS (31)	5.2	VT-NS (8)
15	10.8	1.3	VT-S	15.4	5.6	VT-S	6.5	NI
16	10.0	1.2	VT-NS (8)	9.1	3.7	VT-S	4.4	VT-S
17	9.8	1.9	VT-S	8.8	4.2	VT-S	6.3	NI
18	13.8	1.7	VT-S	13.6	10.1	VT-S	5.6	NI
19	12.9	1.1	NI	11.9	5.2	VT-S	5.3	VT-S
20	12.5	1.4	NI	10.0	6.2	VT-NS (16)	5.2	VT-S
Mean ± SD	11.3 ±2.1	1.4 ±0.3		11.7 ±3.4	7.1 ±2.9		5.4 ±0.8	

NAPA = N-acetylprocainamide; NI = no inducible ventricular tachycardia; PA = procainamide; PVS = programmed ventricular stimulation; Q = quinidine; SD = standard deviation; VT-NS = nonsustained ventricular tachycardia; VT-S = sustained VT.

2 right ventricular sites, at 2 paced cycle lengths, at 2 and 5 times diastolic threshold. Rapid ventricular burst pacing was also performed for 8 to 10 beats at cycle lengths of 60 to 250 ms in 50-ms decrements. The endpoint of stimulation was the induction of sustained ventricular arrhythmias (see definitions) or ventricular refractoriness.

Intravenous procainamide: After documentation of reproducibly inducible sustained VT, all patients received intravenous procainamide in a dose of 10 to 15 mg/kg at a rate of 30 to 50 mg/min. The mean dose of procainamide administered was 1,290 ± 300 mg (range 850 to 1,800). After the infusion was completed, repeat ventricular stimulation was performed using the protocol described herein. Again, stimulation was continued until VT was induced or ventricular refractoriness was reached. When the study was completed a serum sample was taken to measure procainamide and N-acetylprocainamide levels using a fluorescein polarization immunoassay.[8]

Oral procainamide and oral quinidine: After completion of the initial study, patients were randomly assigned to receive either oral procainamide or oral quinidine sulfate treatment with repeat ventricular stimulation after achieving therapeutic serum levels. All patients received both drugs in a sequential manner. The mean procainamide dose was 6.4 ± 1.7 g/day (range 3.0 to 9.0). The mean quinidine dose was 2.8 ± 0.4 g/day (range 2.4 to 3.6). Both drugs were administered for 48 to 96 hours, at which time repeat programmed ventricular stimulation was performed using the same stimulation protocol that was used in the initial study. Serum samples were obtained before programmed ventricular stimulation to document therapeutic levels, and at the completion of each study, for procainamide and quinidine levels, respectively, using a fluorescein polarization immunoassay.[8]

Definitions: *Sustained VT*—VT more than 30 seconds in duration or that required termination because of hemodynamic collapse. *Nonsustained VT*—VT longer than 6 beats that terminated spontaneously within 30 seconds. *Inducible VT*—VT induced at least twice during programmed ventricular stimulation. *Positive drug response*—inability to induce more than 10 beats of VT after administration of procainamide or quinidine.[9] *Negative drug response*—ability to induce more than 10 beats of VT after administration of procainamide.

Statistics: Statistical analysis was performed using Fisher's exact test, and Students *t* test for paired and unpaired data. A p value <0.05 was considered statistically significant.

Results

Response to antiarrhythmic agents: The results of programmed ventricular stimulation after drug administration are summarized in Table I. Six of 20 patients (30%) had a positive drug response (i.e., induction of less than 10 beats of VT) after administration of intravenous procainamide. Three other patients had inducible nonsustained VT longer than 10 beats. Eleven patients (55%) continued to have inducible sustained VT after intravenous procainamide. Five patients (25%) had a positive drug response to oral procainamide. Three patients had inducible nonsustained VT longer than 10 beats, whereas 12 patients (60%) continued to have inducible sustained VT.

Ten patients (50%) had a positive drug response to oral quinidine. Ten patients (50%) continued to have inducible sustained VT after oral quinidine therapy.

Antiarrhythmic drug concentrations: The mean procainamide concentration after the administration of intravenous procainamide was 11.3 ± 2.1 μg/ml, and 11.7 + 3.5 μg/dl after oral therapy. The mean quinidine concentration after the oral administration of quinidine was 5.4 ± 0.8 μg/ml. The mean procainamide concentration after intravenous procainamide was 10.7 ± 1.7 μg/ml in patients with a positive drug response and 11.5 ± 2.2 μg/ml in patients with a negative drug response (difference not significant [NS]). The mean procainamide level after oral administration of the drug was 12.5 ± 3.7 μg/ml in patients with a positive drug response and 11.1 ± 3.4 μg/ml in patients with a negative

drug response (NS). The mean quinidine concentration after oral quinidine therapy was 5.4 ± 0.7 μg/ml in patients with a positive drug response and 5.4 ± 1.0 μg/ml in patients with a negative drug response (NS).

Concordance of drug response: Figure 1 illustrates the concordance of drug response as assessed by programmed ventricular stimulation. Of the 6 patients with a positive drug response to intravenous procainamide, 3 had a positive drug response to oral procainamide and 3 had a negative response. Of the 14 patients with a negative drug response to intravenous procainamide, 2 had a positive response to oral procainamide and 12 had a negative response. Thus, 15 patients (75%) had a concordant drug response for intravenous and oral procainamide and 5 (25%) had a discordant response. Of the 6 patients with a positive drug response to intravenous procainamide, 3 had a positive response to oral quinidine and 3 had a negative response. Seven of the 14 patients with a negative drug response to intravenous procainamide had a positive response to oral quinidine and 7 had a negative response. Thus, 10 patients (50%) had a concordant drug response for intravenous procainamide and oral quinidine. Of the 5 patients with a positive drug response to oral procainamide, all 5 had a positive response to oral quinidine. Of the 15 patients with a negative drug response to oral procainamide, 5 had a positive response to oral quinidine and 10 had a negative response. Thus, 15 patients (75%) had a concordant drug response for oral procainamide and oral quinidine and 5 patients (25%) had a discordant drug response.

Discussion

We have evaluated the ability of intravenous procainamide to predict the efficacy of both oral procainamide and oral quinidine in the treatment of patients with sustained VT. The efficacy of intravenous and oral procainamide was 30% and 25%, respectively. This rate of positive drug response with procainamide is similar to that reported by other investigators.[10,11] The mean serum procainamide levels were 11 to 12 μg/ml and represent realistic target serum levels for such patients.

The rate of positive drug response after oral quinidine therapy was 50%. Previous studies have reported a rate of drug efficacy for quinidine of 24 to 34% in the treatment of patients with VT.[3,12,13] This greater degree of success achieved with quinidine in our study may, in part, be a result of the higher serum levels achieved. The mean serum quinidine level in this study was 5.4 ± 0.8 μg/ml. DiMarco et al[13] reported a 34% success rate in preventing the inducibility of VT using quinidine with a mean serum level of 2.9 ± 0.8 μg/ml. The substantially higher serum levels of quinidine in our study were achieved without a high incidence of untoward side effects. The assay used in this study is comparable in accuracy to that of other techniques.[14] This assay measures a total serum quinidine level, including metabolites such as dihydroquinidine. High-dose quinidine therapy in these patients, with target serum levels of 4 to 6 μg/ml, may result in a greater degree of drug efficacy than more standard dosages, in a fashion analogous to that of Greenspan et al,[11] with respect to high-dose procainamide therapy.

We found a 75% concordance in drug response between intravenous and oral procainamide. Marchlinski et al[10] found a 100% degree of concordance between intravenous and oral procainamide when comparable serum concentrations (within 3 μg/ml) were achieved. Four of the 5 patients in our study with a discordant response had comparable serum levels (within 3 μg/ml) after intravenous and oral therapy. Differences in stimulation protocols, definition of drug efficacy, and patient population between this study and that of

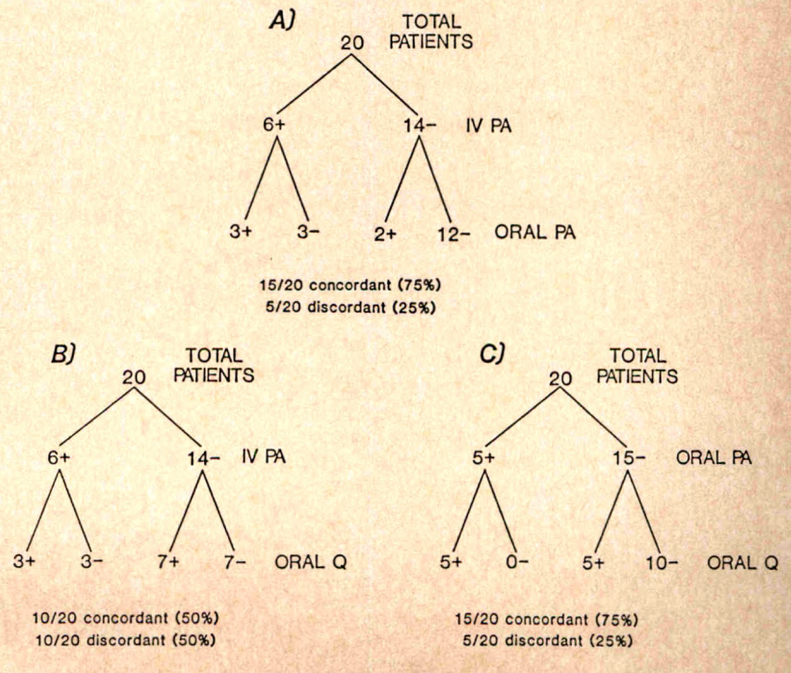

FIGURE 1. Effects of intravenous (IV) procainamide (PA), oral PA and oral quinidine (Q) on inducible ventricular tachycardia (VT) in 20 patients. **A**, intravenous PA compared with oral PA. **B**, intravenous PA compared with oral Q. + = positive drug response, defined as fewer than 10 beats of induced VT; − = negative drug response, defined as more than 10 beats of induced VT.

Marchlinski et al may contribute to differences in results.

A greater degree of discordance was found when comparing the drug responses to intravenous procainamide and oral quinidine treatment. There was a 50% rate of discordance between these 2 agents. Seven of 14 patients who failed to respond to intravenous procainamide had a positive drug response to quinidine. Waxman et al[12] reported only 2 of 42 successful drug trials with quinidine in patients whom intravenous procainamide had failed to prevent inducibility. Again, differences in serum levels may account for these findings. The mean serum quinidine level in the study by Waxman et al was 4.2 ± 1.3 μg/ml in patients with inducible VT and 3.5 ± 1.7 μg/ml in patients without inducible VT. In our study the mean serum quinidine level was 5.4 ± 0.7 μg/ml in patients with a positive drug response and $5.4 + 1.0$ μg/ml in patients with a negative drug response. The higher and more uniform serum quinidine levels in our study patients may explain our higher success rate using quinidine to abolish inducible VT.

Recently, other studies of the inability of procainamide to predict success with other antiarrhythmic drugs have been reported. Rae et al[15] found that 17% of patients with sustained VT and a negative drug response to procainamide went on to have successful prevention of VT induction with other antiarrhythmic drugs. In patients with ventricular fibrillation or nonsustained VT, this rate of success, despite procainamide failure, was 47% and 58%, respectively. Fogoros and Fiedler[16] found a 26% discordance between procainamide and other standard antiarrhythmic drugs in patients with inducible VT or fibrillation, with the bulk of the discordance owing to the efficacy of phenytoin. In our study much of the discordance was a result of the success of quinidine therapy.

Acute drug testing with intravenous antiarrhythmic drugs in patients with VT, may give misleading results with respect to the efficacy of oral agents. The presence of active metabolites that accumulate during oral therapy as well as myocardial concentration of drug during chronic oral therapy may all contribute to differences in drug effects between intravenous and oral therapy.[17–19] The ability to extrapolate or predict the efficacy of oral therapy from the response to acute intravenous administration of a drug is hampered by these factors, whether comparing 2 forms of the same drug or 2 different drugs in the same class. In the current study a 25% discordance of drug response was found between intravenous and oral procainamide and a 50% discordance between intravenous procainamide and oral quinidine. Moreover, our data suggest the importance and efficacy of high-dose quinidine therapy in the management of patients with sustained VT.

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Spectrum of Antiarrhythmic Response to Encainide

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Encainide is effective in suppressing non-life-threatening ventricular arrhythmias; however, inconsistent results have been noted in patients with more serious ventricular arrhythmias. Thirty-seven patients with drug-resistant ventricular arrhythmias were studied. Patients in group I (n = 11) had sustained ventricular tachycardia and those in group II (n = 26) had nonsustained ventricular arrhythmias. In group I, 8 patients had remote myocardial infarction, congestive heart failure and sustained ventricular tachycardia requiring repeated cardioversion (group Ia). None of these patients responded to encainide treatment, but 6 did have an antiarrhythmic response (complete in 3 and only partial in 3) to other investigational antiarrhythmic agents. Three patients in group I, all without ischemic heart disease (group Ib), had an excellent antiarrhythmic response to encainide, as did 21 of 26 patients in group II. In 4 of 5 patients in group II who did not respond, the dosage was limited due to the development of sinus pauses, atrioventricular block or bundle branch block, and in 3 of these 4 patients preexisting conduction disease was evident (PR longer than 0.2 second or QRS longer than 0.12 second). Diplopia occurred while taking the maximal oral dosage in the fifth patient. At 21.5 months of follow-up, 14 of the original 24 patients who responded to encainide continue to receive it; 3 have died (all due to natural progression of left ventricular dysfunction) and encainide was discontinued in 7: in 2 because of syncope, in 2 because of new-onset atrial fibrillation, in 1 patient because of exercise-induced polymorphic ventricular tachycardia, in 1 because of diplopia and in 1 because of skin exanthem.

Paradoxical worsening of ventricular arrhythmias occurred more frequently ($p < 0.01$) in patients in group Ia (4 of 8 patients) than in those in group Ib and II (3 of 29 patients). Although no significant relation could be established, paradoxical responses tended to be associated with higher encainide concentrations and greater prolongation of the QRS interval.

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Encainide is an investigational drug that is effective in suppressing ventricular premature complexes (VPCs) and nonsustained ventricular tachycardia.[1–5] However, inconsistent efficacy has been noted in the treatment of more malignant ventricular arrhythmias. Mason et al[6] reported their experience in the treatment of 38 patients with recurrent, drug-resistant ventricular tachycardia and concluded that encainide was safe, well tolerated and often effective. However, we[7] and others[8,9] have noted paradoxical worsening of ventricular arrhythmias (both spontaneous and those induced by programmed electrical stimulation) during encainide treatment. Likewise, Winkle et al[9] noted that patients with malignant ventricular arrhythmias have the highest incidence of these paradoxical events. These discrepancies may be expected when any agent is used to treat ventricular arrhythmias of widely differing clinical severity, associated cardiac pathologic characteristics and mechanism. An understanding of the characteristics of patients least likely to respond to encainide and, more important, those with a greater risk for adverse effects would allow more effective selection of patients for treatment. We present our experience in 37 patients with drug-resistant ventricular arrhythmias.

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Methods

Thirty-seven patients with high-frequency, complex and symptomatic ventricular arrhythmias who were nonresponsive or intolerant to conventional antiarrhythmic agents were included in this study. Conventional antiarrhythmic agents were considered ineffective if (1) computerized analysis of 12 to 24 hours of electrocardiographic data documented lack of sustained arrhythmia suppression (defined as less than 30% of baseline) or persistence of symptomatic arrhythmias when plasma drug concentrations were in the range usually associated with efficacy; (2) ventricular tachycardia (3 or more

TABLE I Patient Characteristics

	Group Ia	Group Ib	Group II
No. of pts (M/F)	8 M	3 F	26 (18 M, 8 F)
Age (yr)	58 ± 6.4	33 ± 16	56 ± 13
Arrhythmias*			
Sustained VT	All	All	None
Nonsustained VT	All	All	21
VPCs/hr	128 ± 156	2,712 ± 1,885	478 ± 452
Couplet frequency	111 ± 136	7 ± 6	2 ± 4
VT frequency	1 ± 7	315 ± 365	0.4 ± 6
Diagnosis			
Coronary artery disease	All	0	7
No known structural disease	0	3	10
Hypertensive heart disease	0	0	4
Mitral valve prolapse	0	0	3
Cardiomyopathy	0	0	1
Renal failure	0	0	1
Previous antiarrhythmic agents			
Resistant to agents†	5.1 ± 1.5 (range 3–8)	6.3 ± 2.0 (range 3–9)	4.2 ± 2.0 (range 2–11)
LV dysfunction			
NYHA class III–IV	All	0	5
Conduction disorders			
History of 3° AV block	1	0	0
Sinus pauses	1	0	0
QRS 0.12 second	3	0	2
PR 0.20 second	1	0	4
Bundle branch block	0	0	1

* Mean ± standard error of the mean.
† Mean ± standard deviation.
AV = atrioventricular; LV = left ventricular; NYHA = New York Heart Association; VPCs = ventricular premature complexes; VT = ventricular tachycardia.

consecutive VPCs at a cycle length of less than 600 ms) persisted on a maximal, well tolerated dosage during ambulatory monitoring; (3) intolerable side effects or allergy developed that necessitated the discontinuation of therapy; or (4) therapy with a given agent was contraindicated. All patients had received antiarrhythmic therapy with quinidine, procainamide, propranolol and disopyramide (unless such therapy was contraindicated) without satisfactory response. VPC and ventricular tachycardia frequency were quantitated at baseline (24 to 48 hours of data at least 4 elimination half-lives after discontinuation of all previous antiarrhythmic therapy, if possible) and during therapy with gradually increasing dosages of encainide. The QRS duration was monitored at baseline and while encainide dosages were gradually increased. The endpoints of therapy were efficacy, paradoxical worsening of ventricular arrhythmia frequency or other manifestation of toxicity. Encainide was initially administered either intravenously or orally. Because antiarrhythmic efficacy had previously been observed over a wide range of dosages[1,2] and because details of an effective encainide infusion were not available at that time, each infusion was individually designed using the principles outlined herein (gradually increasing dosages of encainide, exploring the dose-response relations). The intravenous infusions of encainide (provided by Mead Johnson Pharmaceuticals) were given at 1 to 2 mg/min over 1 to 2 hours (from 50 to 240 mg), and this infusion rate was continued until efficacy or side effects occurred. If a patient responded to intravenous encainide, the infusion was discontinued and replaced with gradually increasing oral dosages of encainide (supplied as 25- and 50-mg tablets). If patients did not respond to intravenous encainide, the oral preparation was not assessed. Encainide therapy did not always begin with intravenous treatment; many patients received gradually increasing dosages of oral medication (with the same endpoints). The oral dosage schedule was to give encainide every 6 hours and dosage increments were considered only after 48 hours on a stable dosage (beginning at 12.5 mg to a maximum of 125 mg every 6 hours) in all patients with nonsustained ventricular arrhythmias (group II). However, in patients with sustained ventricular tachycardia with ischemic heart disease (group Ia), the schedule was individualized based on clinical urgency. Even so, the dosage schedule was every 6 hours in 5 of 8 patients in group Ia. In 3 patients in group Ia, encainide was given every 3 to 4 hours, for several dosages. Dosages were increased every 12 to 18 hours in patients in group Ia.

Arrhythmia frequency: Arrhythmia frequency was quantified using a Hewlett Packard computerized arrhythmia analysis system (HP 78220) located in the coronary care unit, or the electrocardiographic data were recorded on 8-track FM magnetic tapes using a Honeywell Model 96 FM recorder. Tapes were then analyzed by a computer operator using a PDP 11/60 laboratory minicomputer and a previously described and validated system.[10] This system records the number of VPCs and episodes of ventricular tachycardia using a template matching algorithm. Sustained ventricular tachycardia in this study is defined as more than 100 consecutive VPCs at a cycle length of less than 600 ms.

Electrophysiologic studies: Eleven patients were studied using conventional programmed electrical stimulation techniques. The ventricular origin of the patient's arrhythmias was confirmed by His bundle recordings. A Medtronic model 5652 stimulator was used to pace the right ventricle at a cycle length (S_1S_1) of 500 ms and to introduce up to 2 extrastimuli at twice diastolic threshold. Coupling intervals were serially shortened by 5 ms until sustained ventricular tachycardia occurred or ventricular refractoriness was encountered. If sustained ventricular tachycardia could not be elicited with the electrode catheter positioned at the right ventricular apex, the catheter was moved to the pulmonary outflow tract and the protocol was repeated. This same protocol was used with the patient in the drug-free state and during encainide treatment.

Analytical: Plasma serum samples were assayed using a high-performance liquid chromatography system described by Mayol and Comer,[11] which separates and quantifies encainide, O-demethyl encainide and other metabolites (N-demethyl encainide, O, N-didemethyl encainide and 3-methoxy-O-demethyl encainide). This assay was modified to use S-15531 (supplied by Riker Laboratories) as an internal standard.

Results

Table I describes the population studied. Patients in group I had sustained ventricular tachycardia; 8 patients (group Ia) had previous myocardial infarction and sustained ventricular tachycardia that would not self-terminate and required repeated cardioversions, and 3 patients (Group Ib) had no previous myocardial infarction or coronary artery disease and sustained ventricular tachycardia that did self-terminate). Group II consisted of 26 patients with symptomatic, complex, nonsustained ventricular arrhythmias: 21 with episodes of nonsustained ventricular tachycardia, defined as 3 to 100 consecutive ventricular beats at a cycle length of shorter than 600 ms) and 5 patients with recurrent ventricular couplets but no evidence of ventricular tachycardia.

Response to encainide therapy: None of the patients in group Ia had a satisfactory response to en-

cainide therapy, and in 4 patients ventricular arrhythmias actually worsened. However, 2 of these patients had had paradoxical increases in arrhythmia frequency with other antiarrhythmic drugs, 1 with mexiletine and 1 with aprindine.

One patient in group Ia died while taking encainide (intractable ventricular fibrillation). Of the other 7 patients in groups Ia, no effective therapy could be found for 1, who died in hospital on other medications, and 6 patients finally responded to other antiarrhythmic agents. Response was complete in 3 patients (procainamide-dilantin combination in 2 and bretylium in 1) and only partial in 3 (ventricular tachycardia became much less frequent and slower). Complete responders have been arrhythmia-free for 26 months. During follow-up of the 3 patients with a partial response, 1 died (during procainamide treatment) and 2 patients continued to have episodes of sustained ventricular tachycardia during a 12-month follow-up (receiving procainamide-dilantin combination treatment).

Twenty-four of the 29 remaining patients (group Ib and group II) had an excellent antiarrhythmic response (defined as abolition of ventricular tachycardia and more than 85% suppression of VPCs) and were discharged with encainide therapy. Side effects prevented therapy in 5 patients: in 2 bundle branch block developed, 1 had AV nodal Wenckebach periodicity and 1 had sinus pauses. Before encainide treatments, 3 of these 4 patients had preexisting conduction abnormalities (PR longer than 0.2 second or QRS longer than 0.12 second). In the other nonresponding patient, diplopia developed at maximal allowable dosages of encainide (125 mg orally every 6 hours), and the patient was subsequently shown not to produce the metabolite, O-demethyl encainide. Fourteen of the original 24 responding patients continue to receive encainide at a mean follow-up of 21.5 months (range 1 to 40). Three patients in group II died, all of whom had poor left ventricular function (mean ejections fraction 32%); their deaths were not sudden and were preceded by progressive congestive heart failure. Encainide was discontinued in 7 other patients during follow-up: in 2 because of outpatient syncopal episodes associated with right bundle branch block (no arrhythmia could be documented during prolonged ambulatory monitoring), in 1 because of exercise-induced polymorphic ventricular tachycardia (not present during placebo), in 2 because atrial fibrillation developed, in 1 because of diplopia, and in 1 because of a skin exanthem.

Worsening of arrhythmias: Arrhythmias worsened in 7 patients: 4 in group Ia and 3 in groups Ib and II ($p < 0.01$, χ^2 test). Paradoxical worsening of arrhythmias was identified by the presence of 1 of 4 criteria: (1) Four patients in group Ia showed a striking increase in the frequency of spontaneous episodes of sustained ventricular tachycardia. One of these patients died with intractable ventricular fibrillation and 3 patients had sustained ventricular tachycardia that persisted for hours. (2) In 2 of 11 patients studied (1 patient in group Ia and 1 in group II), sustained ventricular tachycardia was easier to induce by programmed electrical stimulation. All patients appeared to have suppression of spontaneous arrhythmias at the time of electrophysiologic study; however, patients in group Ia had sporadic arrhythmias and spontaneous ventricular tachycardia occurred late during encainide treatment that was unrelated to programmed electrical stimulation. Sustained ventricular tachycardia resulted from the application of 2 extrastimuli in all 3 patients in group Ia at baseline. This same endpoint could still be induced in all 3 patients during encainide treatment, but in 1 patient only 1 extrastimulus was required. In none of the patients in group II was sustained ventricular tachycardia induced at baseline, but in 1 patient it was induced during encainide treatment. (3) In 3 of 4 patients in whom sustained ventricular tachycardia could be terminated with ventricular burst pacing (all in group Ia), this technique was no longer successful during encainide treatment. (4) Nonsustained ventricular tachycardia developed during treadmill exercise testing in 3 of 8 patients in group II who underwent this evaluation during encainide treatment. No patient in group II had had ventricular tachycardia during exercise testing while receiving placebo or antiarrhythmic treatment other than encainide.

TABLE II Relation Between Presence or Absence of Paradoxical Worsening of Arrhythmias in Group Ia to Dosage, Plasma Concentration and Electrocardiographic Interval Change

	Paradoxical Events (n = 4)	VT Nonresponsive (n = 4)
Mean dose (mg/day)	300 ± 90 (range 181–400)	284 ± 67 (range 200–362)
Encainide conc. (ng/ml) when treatment stopped	977 ± 847 (range 81–1,765)	191 ± 141 (range 31–302)
ODME conc. (ng/ml) when treatment stopped	458 ± 481 (range 24–977)	NA
Change in QRS duration (sec) from baseline	0.06 ± 0.03 (range 0.04–0.11)	0.04 ± 0.02 (range 0.01–0.05)
Change in QTc interval (sec) from baseline	0.03 ± 0.05 (range 0.03–0.08)	0.11 ± 0.08 (range 0.05–0.16)
Change in JTc interval (sec) from baseline	0.05 ± 0.02 (range 0.03–0.07)	0.07 ± 0.07 (range 0.03–0.19)

conc. = concentration; NA = not available; ODME = O-demethyl encainide; VT = ventricular tachycardia.

Dosage, concentration, electrocardiographic interval changes and outcome in group Ia: Table II lists the presence or absence of paradoxical events occurring in group Ia related to dosage, plasma concentration and electrocardiographic interval change. Patients in whom paradoxical events developed tended to have higher plasma encainide concentrations and greater prolongation in the QRS duration. However, owing to the small number of patients, no significant relationships could be found.

Discussion

Although encainide is often effective in the treatment of drug-resistant ventricular arrhythmias, we have identified a subset of patients in whom encainide therapy is uniformly not successful and in whom adverse effects occur frequently. Although lack of response to encainide may imply drug resistance, 6 patients had a complete or partial antiarrhythmic response to other

medications. Paradoxical worsening of arrhythmias was not observed during optimal antiarrhythmic therapy. Disparity in antiarrhythmic efficacy among patient subsets may relate both to the nature of the underlying myocardial abnormality and the presumed mechanism of the arrhythmia being treated. The state of the underlying myocardium clearly influences the electrophysiologic effects of a given medication, as shown by the differing electrophysiologic effects of procainamide and lidocaine in normal and in ischemic myocardium.[12–14] Similarly, the postulated mechanism of the arrhythmia being treated can alter efficacy. Several antiarrhythmic agents show a lack of efficacy or paradoxical worsening of reentrant arrhythmias while effectively suppressing automatic arrhythmias.[15–18] We examined the effect of O-demethyl encainide (the active metabolite of encainide) on spontaneous arrhythmias (presumably increased automaticity) and electrically induced arrhythmias (presumably reentrant) occurring 2 days after occlusion-reperfusion injury in dogs.[19] Spontaneous arrhythmias were effectively suppressed, whereas the ability to induce sustained ventricular tachycardia by programmed electrical stimulation was enhanced and ventricular fibrillation threshold was lowered. In contrast, O-demethyl encainide raised the ventricular fibrillation threshold in normal animals. The results seen in the present study in humans are in keeping with these observations in animals. Although encainide appears to be effective in treating many patients with drug-resistant ventricular arrhythmias (with a spectrum of myocardial abnormalities and arrhythmic mechanisms), patients with sustained ventricular tachycardia associated with previous myocardial infarction constitute a subset of patients who do not respond to encainide and in whom paradoxical worsening of arrhythmias occurs frequently. Patients who have sustained ventricular tachycardia associated with segmental wall motion abnormalities have been found to have delayed and nonhomogeneous intraventricular conduction in the border of infarct zones.[20–22] Myocardial abnormalities that predispose to nonhomogeneous intraventricular conduction combined with medications that markedly delay intraventricular conduction (encainide and O-demethyl encainide) may create conditions ideal for the development of reentry circuits.[7]

Mason et al[6] reported their experience in 38 patients with drug-resistant ventricular tachycardia and reported results that contrast with ours. All of their patients were initially considered responsive to encainide therapy, although 17 were withdrawn from encainide during the first 6 months of follow-up. The clinical characteristics of patients who did not have a persistent outpatient antiarrhythmic response were not detailed. In their study, the 4 patients who had paradoxical worsening of ventricular arrhythmias with encainide also had previously received repeated cardiopulmonary resuscitation.

The manner in which encainide is administered may also affect the resultant incidence of efficacy or toxicity. Given the information that encainide had a half-life of less than 3 hours in most patients, the dosage of encainide was at times rapidly increased in this study to control life-threatening ventricular arrhythmias. However, new analytic techniques have allowed the identification of metabolites of encainide[11] that appear to contribute to the pharmacologic effects of encainide (electrophysiologic effects[19,23,24] antiarrhythmic response[25–27] and possible adverse effects[19]). These active metabolites of encainide appear to have delayed elimination dosage relative to the parent, and rapid increases in encainide dosage (before reaching steady-state conditions for the metabolites) may result in delayed excessive accumulation of the metabolites. This may explain the paradoxical worsening of ventricular arrhythmias often seen in patients with life-threatening arrhythmias. In support of this possibility we showed that a high concentration (more than 300 ng/ml) of O-demethyl encainide (the predominant metabolite in most patients[28]) lowers the fibrillation threshold in an ischemic canine model[19] and predisposes to ventricular tachycardia induced by programmed electrical stimulation (presumably a reentrant mechanism). Owing to its complex metabolic profile, encainide appears ill-suited as an intravenous agent for treating life-threatening ventricular arrhythmias. Dosage increases of encainide should be considered only after steady-state conditions have been achieved for both the parent compound and its metabolites (several days).

In the present study relatively few patients with sustained ventricular tachycardia were evaluated during encainide treatment. If more patients had been studied, a proportion of patients (like those in group Ia) might have responded to encainide. However, because paradoxical worsening of arrhythmia was frequent and alternative medications were effective, additional patients like those in group Ia were not treated with encainide.

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Exercise-Induced Left Bundle Branch Block and Its Relation to Coronary Artery Disease

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The records of 2,584 consecutive patients who underwent both treadmill exercise testing and coronary cineangiography were reviewed to determine the relation between exercise-induced, acceleration-dependent left bundle branch block (LBBB) and the presence of coronary artery disease (CAD). Rate-dependent LBBB during exercise was identified in 28 patients (1.1%), who were categorized according to their presenting symptoms: classic angina pectoris, atypical chest pain, symptomatic cardiac arrhythmia and asymptomatic. Asymptomatic patients underwent a screening exercise test. CAD was present in 7 of 10 patients who presented with classic angina pectoris, but 12 of 13 patients presenting with atypical chest pain had normal coronary arteries. All 10 patients in whom LBBB developed at a heart rate of 125 beats/min or higher were free of CAD, whereas 9 of 18 patients in whom LBBB developed at a heart rate of less than 125 beats/min had CAD. Normal coronary arteries were present in 3 patients who presented with angina and in whom both chest pain and LBBB developed during exercise. It is concluded that (1) patients who present with atypical chest pain in whom rate-dependent LBBB develops on the treadmill are significantly less likely to have CAD than patients who present with classic angina; (2) the onset of LBBB at a heart rate of 125 beats/min or higher is highly correlated with the presence of normal coronary arteries, regardless of patient presentation; and (3) patients with angina in whom both chest pain and LBBB develop during exercise may have normal coronary arteries.

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The clinical significance of acceleration-dependent, exercise-induced left bundle branch block (LBBB) is controversial. Several investigators[1–4] have documented the coexistence of acceleration-dependent LBBB during stress testing and angiographically normal coronary arteries. However, Wayne et al[5] suggested that exercise-induced LBBB is almost always associated with demonstrable cardiac abnormalities, most frequently coronary artery disease (CAD).[5] To further evaluate these conflicting observations we reviewed the records of 2,584 consecutive patients at our institution who underwent treadmill exercise testing, left ventriculography and coronary cineangiography. We identified 28 patients (1.1%) who had acceleration-dependent LBBB during stress testing. This study examines the relation between exercise-induced, rate-dependent LBBB and the presence and extent of CAD in these patients.

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Methods

Standard criteria were used to define complete LBBB, including a QRS duration of 0.13 second or longer. Normal conduction was recorded on the electrocardiogram at rest before the initiation of exercise testing in all patients. We required that LBBB result from an acceleration of the heart rate and not a single premature stimulus.

Treadmill exercise testing was performed using a modified Balke protocol. Coronary cineangiography was carried out using the Judkins technique. All single-plane left ventriculograms were recorded in the right anterior oblique position. Left ventricular function was evaluated by segmental wall motion analysis of the ventriculograms and was considered abnormal if any 1 segment demonstrated abnormal systolic motion. Significant coronary artery disease was defined as at least a 50% reduction in the luminal diameter of the left anterior descending, left circumflex, left main or right coronary arteries.

Statistics: The relation between presenting symptoms and the presence or absence of CAD was assessed using Fisher's exact test, as was the relation between heart rate at the onset of LBBB and the presence or absence of CAD.

Patients: Table I is a list of the initial indication for exercise testing, medications at the time of testing, and the results of treadmill testing, coronary cineangiography and left ventriculography. In all 28 patients complete LBBB developed during exercise testing. The initial treadmill exercise test is reported in instances where patients had more than 1 stress test, except in cases where LBBB occurred only during a single, subsequent examination. Among the 8 patients who underwent more than 1 test, 4 had LBBB only 1 time, whereas 2 showed aberrant conduction at nearly identical heart rates

TABLE I Results of Left Ventriculography, Coronary Cineangiography and Treadmill Exercise Testing (TME)

Indication for TME	Sex & Age (yr)	Medications	RAO Ventriculogram	% Diameter Narrowing				TME		HR at Onset of LBBB	Chest Pain
				LM	LAD	LC	Right	Duration	Peak HR (beats/min)		
Angina/MI											
	M 62	B,N	Normal	O	O	75	90	6′00″	96	60	+
	M 51	B,N	Diffuse HK	O	100	95	100	8′00″	150	120	+
	M 54	O	AL aneurysm	O	95	O	O	6′00″	145	82	O
	M 52	O	AL, A HK	O	O	O	O	13′00″	145	145	+
	M 65	O	Normal	O	O	O	O	7′23″	143	140	+
	M 58	B,N	Diffuse HK	O	75	20	90	5′23″	143	76	+
	F 70	B,N	Normal	O	20	O	20	4′15″	71	60	+
	F 51	D	Normal	O	O	O	75	2′00″	106	70	+
	M 50	N	AL, A AK	75	90	75	100	10′00″	158	80	O
	M 61	D	Normal	75	O	75	100	3′22″	86	80	+
Atypical chest pain											
	M 64	O	Diffuse HK	O	O	O	O	7′00″	150	150	O
	M 46	O	Normal	O	O	O	O	9′00″	140	140	O
	M 61	O	Normal	O	O	O	O	8′00″	142	115	O
	M 53	N	Normal	O	O	O	O	9′00″	155	73	O
	F 43	B	Normal	O	O	O	O	11′45″	108	108	O
	M 45	DPH	Normal	O	O	O	O	7′00″	167	108	O
	F 42	O	Normal	O	O	O	O	4′10″	146	100	+
	M 55	B	Normal	O	20	25	O	9′00″	136	130	+
	F 62	B	Normal	O	50	O	O	5′00″	125	86	O
	F 52	O	Normal	O	O	O	O	4′30″	154	107	O
	F 38	O	Normal	O	O	O	O	3′00″	154	85	+
	F 48	O	Normal	O	O	O	O	6′00″	167	140	O
	M 43	O	Normal	O	O	O	O	10′00″	143	143	O
Cardiac arrhythmias											
	M 60	B,Q	AL, PB, HK	O	95	90	O	6′37″	123	60	O
	M 54	B,D	Diffuse HK	O	O	O	O	4′59″	170	115	O
	M 29	B,Aprin	A HK	O	O	O	O	3′47″	143	143	O
Asymptomatic screen											
	M 61	O	Normal	O	O	O	O	5′40″	150	140	+
	M 40	O	Normal	O	O	O	O	9′00″	163	163	O

A = apical; AB = anterobasal segment; AK = akinesia; AL = anterolateral segment; Aprin = aprindine; B = β-blocking drug; D = digitalis; DPH = diphenylhydantoin; HK = hypokinesia; HR = heart rate; LAD = left anterior descending coronary artery; LBBB = left bundle branch block; LC = left circumflex coronary artery; LM = left main coronary artery; MI = myocardial infarction; N = long-acting nitrates; PB = posterobasal; Q = quinidine; RAO = right anterior oblique; RCA = right coronary artery; O = none; + = present.

TABLE II Indications for Treadmill Exercise Testing (TME) and Results of Cardiac Catheterization

Indication for TME	No. of Pts	−CAD Nl LV	−CAD Abnl LV	+CAD Nl LV	+CAD Abnl LV
Angina/MI	10	2	1	3	4
Atypical chest pain	13	11	1	1	0
Cardiac arrhythmias	3	0	2	0	1
Asymptomatic screen	2	2	0	0	0
Total	28	15	4	4	5

Abnl LV = at least 1 area of abnormal wall motion on right anterior oblique (RAO) ventriculogram; CAD = coronary artery disease; +CAD = at least 1 vessel with ≥50% stenosis; −CAD = no lesion with ≥50% stenosis; MI = myocardial infarction; Nl LV = normally contracting left ventricle on RAO ventriculogram.

TABLE III Indication for Treadmill Exercise Test (TME) and Presence or Absence of Coronary Artery Disease

Indication for TME	No. of Pts	+CAD	−CAD	
Angina/MI	10	7	3	p <0.004
Atypical chest pain	13	1	12	
Cardiac arrhythmias	3	1	2	
Asymptomatic	2	0	2	
Total	28	9	19	

CAD = coronary artery disease; +CAD = at least 1 vessel with ≥50% stenosis; −CAD = no lesion ≥50%; MI = myocardial infarction.

and 2 at significantly slower heart rates during repeat testing. All patients were white; 19 were men and 9 were women. They were 29 to 70 years old (mean 53).

Patients were classified according to the initial indication for exercise stress testing. These classifications were: (1) patients with typical angina pectoris or previously documented myocardial infarction, (2) patients considered to have atypical chest pain, (3) patients studied for symptomatic cardiac arrhythmias, and (4) asymptomatic patients undergoing a screening exercise test.

Results

Arteriographic studies revealed no significant CAD in 19 of the 28 patients (68%); 15 of those 19 were believed to have normal wall motion by left ventriculography. The left ventriculogram was considered to be normal in 19 of the 28 patients, 4 of whom had significant CAD (Table I). In only 3 patients (11%) did ST-segment changes suggestive of ischemia develop before the onset of LBBB. Repolarization abnormalities were observed in 4 patients after the restoration of normal conduction, although in several patients interpretation of postexercise ST-segment changes were precluded by the persistence of aberrant conduction beyond the 6-minute period of observation.

The extent and location of coronary artery narrowing among the 9 patients with CAD was highly variable (Table I).

The indication for initial treadmill exercise testing and the results of left ventriculography and coronary cineangiography are compared in Table II. Table III is a comparison of the initial indication for exercise testing and the presence or absence of CAD. Significant CAD was present in 7 of 10 patients who had had a prior myocardial infarction or were believed to manifest classic angina pectoris. Only 1 of 13 patients referred for diagnostic evaluation of atypical chest pain had CAD; 11 of these patients also had normal left ventriculographic findings. This difference in the prevalence of CAD between patients with classic angina and patients with atypical chest pain was highly significant ($p < 0.004$). Both of the asymptomatic subjects who underwent arteriographic studies because of an abnormal treadmill exercise test were normal. The ventriculograms were abnormal in all 3 patients with symptomatic cardiac arrhythmias, but only 1 patient had significant CAD.

Figure 1 depicts the relation between the heart rate at the onset of LBBB and the presence or absence of CAD. Whereas aberrant conduction developed at variable heart rates in patients without significant CAD, in all patients with CAD LBBB developed at a heart rate of less than 125 beats/min. Exercise-induced LBBB at a heart rate of 125 beats/min or greater was more likely to develop in patients without CAD ($p < 0.01$).

Chest discomfort developed in 12 of 28 patients during or soon after exercise. Seven of these patients had normal coronary arteries and 5 had significant CAD. No consistent relation was observed between the onset of chest discomfort and the initiation of aberrant conduction during exercise. Normal coronary arteries were found in 3 patients with typical angina or previously documented myocardial infarction in whom chest pain and rate-dependent LBBB developed with exercise.

Discussion

An accurate determination of the clinical significance of exercise-induced, acceleration-dependent LBBB is important. Rate-dependent LBBB may be a reflection of underlying myocardial dysfunction, intrinsic disease of the cardiac conducting tissues or a compromised coronary circulation. Before the advent of coronary arteriography, rate-dependent LBBB was believed to result most often from arteriosclerotic CAD.[6–10] More recently, several investigators have reported patients with exertional chest pain, exercise-induced LBBB and normal coronary arteries.[1,3,4] Conflicting observations have also been reported. Wayne et al[5] found angiographically proved CAD in 7 of 11 patients with exercise-induced LBBB, and 1 other patient had documented coronary spasm. Two patients had primary myocardial disease and only 1 of their patients was considered to be without evidence of cardiovascular disease. They concluded that exercise-induced bundle branch block is almost always associated with cardiovascular disease, and usually with CAD.

Our results help to clarify these contrasting observations and provide a means of identifying patients with exercise-induced LBBB and normal coronary arteries. In our study, of 28 patients with exercise-induced, acceleration-dependent LBBB, 19 (68%) were free of CAD. Coronary cineangiographic results were normal in 12 of 13 patients with atypical chest discomfort. Only 3 of 10 patients with a clinical diagnosis of angina pectoris or a prior myocardial infarction had normal coronary arteries, and only 2 had normal ventriculographic findings as well. Thus, exercise-induced LBBB was associated with abnormal findings at cardiac catheterization in less than half of our patients, although, as one might expect, most patients with classic angina did have significant CAD, whereas patients with atypical chest pain did not. These findings indicate the need to categorize patients with exercise-induced LBBB based on the nature of their presenting symptoms and, as such, reinforce the importance of accurate historical information.

Our study results suggest that the presence of normal coronary arteries can be predicted with increased specificity by examining the exercise heart rate at the onset of aberrant conduction. None of the 10 patients in whom LBBB developed at a heart rate of 125 beats/min or greater had CAD; 7 had normal findings and 3 had segmental wall motion abnormalities on the left ventriculogram at rest. A review of previous reports provides further support for this heart rate criterion. Previous studies[1–5,12] include an additional 23 cases of exercise-induced LBBB in patients undergoing cineangiography; in 6 of these patients LBBB developed at exercise heart rates of 125 beats/min or greater and 5 had normal coronary arteries.

Surprisingly, 3 of 8 patients with classic angina pectoris who had chest pain and LBBB with exercise had normal coronary arteries. All 3 patients with a history of atypical chest pain in whom LBBB and chest discomfort developed during treadmill testing were free of CAD. These findings are consistent with those reported by others.[1,3,4] However, the cause of chest pain in these patients is not known. Virtanen et al[3] reported 7 patients in whom exercise-induced LBBB, chest pain and paradoxical septal motion simultaneously developed, without overt evidence of myocardial ischemia. They proposed that the chest discomfort resulted from abnormal septal motion. Kafka and Burggraf[4] also observed the simultaneous onset of exercise-induced LBBB and chest pain in a patient with no apparent ischemia, but they did not document a coexistent change in septal motion.[4] In our patients there was no consistent relation between the onset of chest discomfort and the onset of left bundle branch aberrancy.

The clinical significance of exercise-induced LBBB also remains poorly defined. Although several investigators suggest that acceleration-dependent LBBB results most often from arteriosclerotic CAD,[6–11] LBBB during exercise clearly occurs in the presence of angiographically normal coronary arteries. Data from the Framingham study indicated that in as many as one-third of patients in whom permanent LBBB develops, clinical congestive heart failure develops a mean of 3.3 years after the onset of LBBB.[13] In many cases the LBBB was the first clinical sign of a developing cardiomyopathy. Exercise-induced LBBB, therefore, may also be an early manifestation of a developing, nonischemic cardiomyopathy.

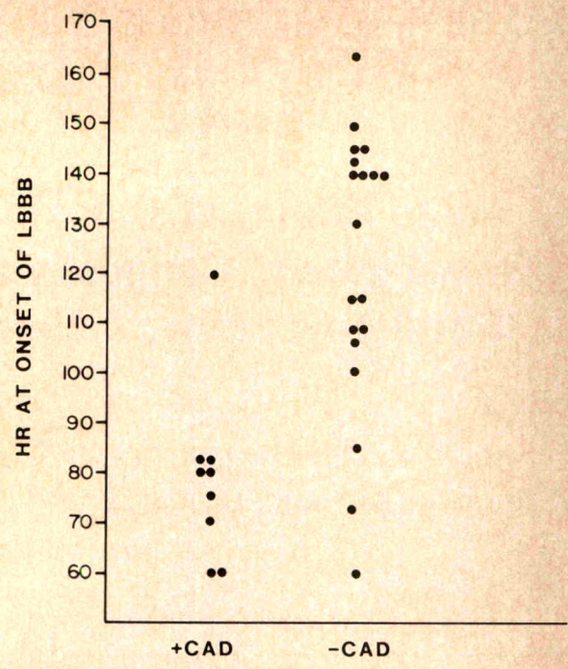

FIGURE 1. Heart rate (HR) at the onset of left bundle branch block (LBBB) relative to the presence or absence of coronary artery disease (CAD). No patient with CAD had exercise-induced LBBB at a heart rate of 125 beats/min or greater.

One limitation of this study is that the data were collected retrospectively. In addition, much of the cardiac catheterization data were derived from subjective visual interpretation by different angiographers, and hence is subject to interobserver variability. Ventriculography alone can legitimately be criticized as an incomplete means of evaluating left ventricular function. Finally, the presence of coronary artery spasm was not definitely excluded in most patients with normal coronary cineangiographic findings.

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Acute Effects of Digoxin on Total Systemic Vascular Resistance in Congestive Heart Failure Due to Dilated Cardiomyopathy: A Hemodynamic-Hormonal Study

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The effects of the digitalis glycosides on systemic vascular resistance (SVR) in patients with congestive heart failure (CHF) are controversial. Most investigators report a reduction in total SVR, an action that has been attributed primarily to withdrawal of elevated sympathetic tone. Direct proof of this hypothesis is lacking, however, and the roles played by the renin-angiotensin-aldosterone and vasopressin systems have not been fully explored. Moreover, in several studies of patients with CHF, SVR did not decrease after the administration of digitalis. To clarify these issues, the hemodynamic and hormonal effects of digoxin were correlated in 11 normotensive men in sinus rhythm with CHF due to dilated cardiomyopathy. Patients were evaluated at rest and during submaximal exercise before and 6 hours after the intravenous infusion of 1.0 mg of digoxin (mean serum concentration 1.7 ng/ml). With digoxin therapy, heart rate, pulmonary wedge pressure and right atrial pressure declined and cardiac output increased. Although vasopressin was unchanged, both plasma norepinephrine concentrations and plasma renin activity decreased, the reduction in norepinephrine correlating with the increase in cardiac output. Despite these hemodynamic and hormonal effects, there was no change in total SVR at rest or during exercise. It is concluded that the improvement in cardiac function with digoxin in this patient group was a result of the inotropic properties of the drug, without an associated reduction in impedance. The failure of total SVR to decrease despite decreases in plasma norepinephrine levels and plasma renin activity might be explained by concomitant digitalis-induced vasoconstriction, impaired ability of arterioles to dilate in CHF, or offsetting alterations in other vasoactive hormone systems.

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The ability of therapeutic agents to improve cardiovascular function relates to their actions on both the peripheral vasculature and the heart. The digitalis glycosides, long recognized as having potent inotropic properties, have also been shown to constrict arterioles in the normal experimental animal[1,2] and to increase vascular resistance in the nonfailing human circulation.[3]

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In contrast, it is generally accepted that digitalis does not cause vasoconstriction in patients with congestive heart failure (CHF). The nature of the resistance response to digitalis in patients with CHF is controversial, however. Most investigators have documented reductions in systemic vascular resistance (SVR),[4–12] leading to the conclusion that the glycosides owe their beneficial effects in patients with CHF both to enhancement of cardiac contractility and to lowering of the impedance to ventricular ejection.[13,14] However, a number of studies have demonstrated no decrease in SVR even when other hemodynamic variables changed considerably.[6,15–19] The reasons for the conflicting data are not known, but may be in large part a result of the complex nature of the CHF syndrome as well as the difficulty in obtaining adequate standardization of clinical parameters in the study population.[15]

It is unclear why drugs that are inherently vasoconstrictive fail to increase, or even reduce, vascular resistance in patients with CHF. The most frequently proposed mechanism is that in addition to their direct vascular effects, the digitalis glycosides mediate a withdrawal of the elevated sympathetic tone characteristic of this syndrome.[4,5,13,20] However, direct proof of this hypothesis is not available, and changes in plasma norepinephrine concentrations after administration of digitalis have not been investigated. A reduction in plasma renin activity (PRA) was recently reported,[21] but the responses to digitalis of the vasopressin system (the activity of which is also increased in patients with CHF[22,23]) have not been explored. Moreover, in no CHF study have changes in vasoactive hormone levels with digitalis been correlated with the hemodynamic actions of the drug.

In view of these uncertainties with regard to the hemodynamic and neurohumoral responses to digitalis in patients with CHF, this study was designed with a 2-fold purpose: to evaluate the acute effects on vascular resistance of therapeutic concentrations of a digitalis glycoside in a well-defined group of normotensive patients with chronic, stable, myocardial failure in sinus rhythm; and to correlate those actions with simultaneous changes in the blood levels of hormones known to affect arteriolar smooth muscle tone. The results indicate that despite significant reductions in the vasoconstrictive hormone levels, there was no change in total SVR in this patient population.

Methods

Criteria for patient selection: The study cohort consisted of 11 men with myocardial failure due to alcoholic or idiopathic cardiomyopathy who fulfilled the following clinical and hemodynamic requirements: typical symptoms of left-sided heart failure, with or without right-sided failure, at least 6 months in duration; radiographic and echocardiographic criteria for cardiomegaly; the presence of normal sinus rhythm; systemic arterial mean pressure greater than 65 mm Hg but less than 110 mm Hg at rest; left ventricular ejection fraction less than 35% as determined by equilibrium radionuclide scanning; cardiac index 2.5 liters/min/m^2 or less; and pulmonary wedge pressure 12 mm Hg or more at rest in the supine position. Reasons for exclusion from the study included pericardial, restrictive or valvular heart disease (except for mild tricuspid or mitral regurgitation thought to be due solely to ventricular dilation); acute exacerbation of heart failure within the previous 4 weeks; endocrinologic disorder, including diabetes mellitus; clinically important pulmonary disease (excluded by pulmonary function studies when necessary); more than mild renal or hepatic dysfunction (creatinine greater than 2.0 mg/dl, bilirubin more than 2.0 mg/dl, serum glutamic oxaloacetic transaminase more than 60 IU/liter); and inability to adhere to the prescribed diet. All patients had either never received digitalis or had had such therapy discontinued for at least 2 weeks.

Stabilization period: Subjects were admitted to the clinical research center 5 to 7 days before the study, at which time all remaining medications, including diuretic drugs, were stopped. No smoking was permitted. A strict metabolic diet providing 33 mEq of sodium and 60 mEq of potassium per day was prescribed (American Dietary Products), and patients were observed until body weights were stable (less than 2% variation) for at least 2 successive days.

Drug intervention: Thirty-six hours before digoxin administration, a balloon-tipped, triple-lumen, thermodilution catheter was advanced to the pulmonary artery under fluoroscopic control, and a short plastic catheter was inserted percutaneously into the radial artery. Subsequent procedures were conducted in a quiet, private room where every effort was made to ensure a minimum of emotional stimulation. In each instance, experimental observations were made at least 3 hours after eating. Twenty-four hours before drug administration, the first of 2 sets of control hemodynamic and hormone measurements was made. Heart rate, cardiac output, and systemic arterial, pulmonary arterial, pulmonary wedge and right atrial pressures were determined in all patients after at least 1 hour of sitting at rest in a comfortable chair. To document stability of the control data, hemodynamic measurements were repeated at intervals of 20 to 30 minutes until there was less than 10% variability in cardiac output. Control hemodynamic variables were then measured during 5 to 10 minutes of pedaling in the sitting position on a bicycle ergometer at a constant load of 15 W (50 rpm). Simultaneous with the rest and exercise hemodynamic studies, venous blood was drawn through the right atrial port of the intracardiac catheter for the determination of plasma concentrations of norepinephrine, epinephrine and arginine vasopressin as well as PRA. To provide insights into the interactions between digitalis and the vasoactive hormones, plasma osmolality and plasma concentrations of sodium and potassium were measured and serum was collected for analysis of aldosterone and adrenocorticotropic hormone (ACTH).

On the morning after these initial studies, baseline hemodynamic and hormonal measurements were repeated. Immediately thereafter (at approximately 12 PM), 1.0 mg of digoxin, diluted to 50 ml in 5% dextrose in water, was infused into the right atrium by infusion pump over a period of 30 to 40 minutes (mean dose 0.015 mg/kg body weight). Six hours later, hemodynamic studies at rest and during exercise were performed for a third time, and blood was again drawn simultaneously for hormonal, osmolality and electrolyte analyses.

Serum digoxin levels were determined in all patients at rest during the second control period and 6 hours after completion of the digoxin infusion. In 8 patients, digoxin levels were also measured 1 hour after infusion.

Hemodynamic techniques: Heart rate was measured directly from a continuously monitored electrocardiogram. Systemic arterial and intracardiac pressures were obtained using Gould P23 Id pressure transducers calibrated against mercury, and were recorded on a multichannel physiologic recorder (Electronics for Medicine model VR6). The reference for all pressures was a plane 5 cm below the sternal angle. Mean pressures were measured using electronic damping. Cardiac output was determined by the thermodilution technique using an Edwards Laboratory computer (model 9520A) and 10-ml injections of iced 5% dextrose in water. Each value represents the average of 3 consecutive injections. In our laboratory, cardiac output measurements are reproducible to within 5%. Total SVR was calculated as [(systemic arterial mean pressure − mean right atrial pressure)/cardiac output] × 80.

Hormonal, digoxin and electrolyte analyses: Blood for chemical determinations was drawn into chilled tubes containing the proper anticoagulant (if any), centrifuged within 10 minutes at 2°C and stored at −80°C until analyzed. Catecholamine levels were measured in the first 2 patients by a radioenzymatic assay (Cat-a-Kit,™ Upjohn Diagnostics) and in the remaining patients by liquid chromatography.[24] Correlation coefficients between the 2 methods are 0.94 and 0.90 for norepinephrine and epinephrine, respectively, and all

TABLE I Patient Group

Pts.	Etiology of CM	Age (yr)	Duration of CHF (mo)	NYHA Class	BSA (m^2)	EF (%)	Supine CI (liters/min/m^2)	Supine PWP (mm Hg)
W.B.	Alcoholic	49	24	3	1.74	10	1.70	27
W.H.	Idiopathic	62	36	3	2.15	18	1.66	27
J.W.	Idiopathic	50	96	3	1.75	22	2.29	12
G.H.	Alcoholic	65	13	3	1.75	28	2.50	26
T.C.	Alcoholic	60	6	3	2.29	22	1.63	27
D.L.	Alcoholic	47	48	3	2.00	12	2.24	17
C.T.	Alcoholic	50	12	3	1.80	19	1.54	31
R.C.	Alcoholic	55	7	3	1.76	15	1.89	14
H.L.	Idiopathic	64	10	3	1.96	24	1.85	15
F.G.	Idiopathic	45	24	3	1.87	16	1.88	28
W.N.	Alcoholic	53	6	2	1.65	15	1.74	12
Mean		55	26	3	1.88	18	1.90	22
±SD		±7	±27	±0	±0.20	±5	±0.31	±7

BSA = body surface area; CHF = congestive heart failure; CI = cardiac index; CM = cardiomyopathy; EF = ejection fraction; NYHA = New York Heart Association; PWP = pulmonary wedge pressure; SD = standard deviation.

values are reported without adjustment for method. PRA was estimated by quantitation of generated angiotensin I (Rianen™ Radioimmunoassay System, New England Nuclear). Concentrations of arginine vasopressin,[25] aldosterone, ACTH and digoxin were determined by radioimmunoassay. There was no cross reactivity between digoxin and any of the hormones tested. Plasma osmolality was determined by freezing point depression (model 3DII osmometer, Advanced Instruments), and plasma electrolytes by flame photometry.

Statistical calculations: Sequential changes in hemodynamic and hormonal variables were evaluated using the 2-tailed *t* test for paired data. Correlation coefficients were established using linear regression analysis of the bivariate normal distribution. Results were considered significant at the 5% level. Except where noted, values are reported as mean ± standard error of the mean.

Results

Patients: Baseline clinical and hemodynamic characteristics of the study subjects are listed in Table I. All patients achieved a stable weight with dietary therapy alone. In no instance did symptoms worsen during the drug-free stabilization period, nor was specific therapy required before hemodynamic intervention.

Hemodynamic findings (sitting position) (Tables II and III): There were no significant differences in hemodynamic measurements between the 2 sets of control observations (data not shown). With digoxin, heart rate decreased significantly both at rest and during exercise. Cardiac output increased an average 13% at rest and 12% during exercise. Systemic arterial mean pressure increased significantly at rest, but pulmonary arterial diastolic, pulmonary wedge and right atrial pressures decreased at both levels of activity. No significant change occurred in total SVR at either rest or with exercise.

Hormonal observations (Tables II and III): There were no significant differences in hormone levels between the 2 sets of control measurements (data not shown). After administration of digoxin, the plasma norepinephrine concentration decreased an average of 28% at rest and 26% during exercise, declining in all instances in which it was measured. Plasma epinephrine did not change. Mean PRA decreased 32% at rest and 50% during exercise. At rest, PRA decreased in 8 patients, increased in 1 patient, and was essentially unchanged in the remaining 2. During exercise, all but 1 patient had a decrease in PRA after administration of digoxin.

The decline in plasma norepinephrine concentration correlated significantly with the increase in cardiac output both at rest and during exercise (Fig. 1). It also correlated with the reduction in mean right atrial pressure ($r = 0.72$, $p < 0.05$ at rest; $r = 0.66$, $p = 0.05$ during exercise). The reduction in PRA correlated with

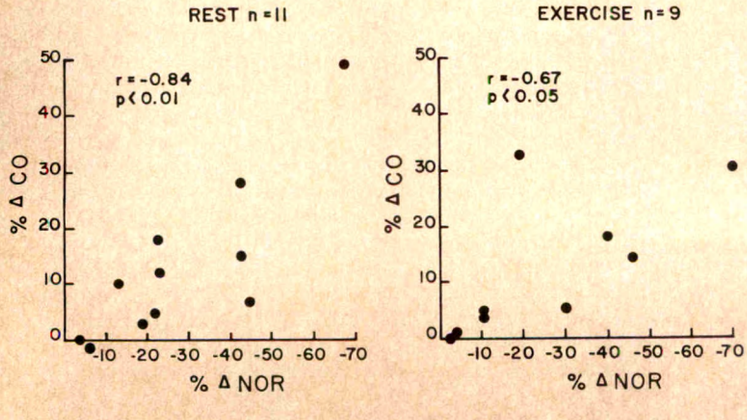

FIGURE 1. Correlations between percentage changes in cardiac output (% ΔCO) and in plasma norepinephrine concentration (% ΔNOR) after digoxin therapy.

TABLE II Hemodynamic and Hormonal Changes at Sitting Rest

Pts.		HR (beats/min)	CO (liters/min)	SA (mm Hg)	PAD (mm Hg)	PWP (mm Hg)	RA (mm Hg)	TSVR (dynes s cm^{-5})	NOR (pg/ml)	EPI (pg/ml)	PRA (ng/ml/hr)	AVP (pg/ml)	ALDO (pg/ml)	ACTH (pg/ml)	DIG (ng/ml)
W.B.	C	102	2.74	68	12	12	0	1,985	1,064	246	3.4	7.0	244	<19	0.0
	D	98	2.89	72	8	8	−2	2,048	826	175	1.5	14.4	324	20	1.5
W.H.	C	91	3.31	88	34	27	12	1,837	642	73	0.4	7.9	204	<19	0.0
	D	87	3.54	89	27	25	3	1,944	353	124	0.2	1.7	180	<19	1.6
J.W.	C	86	3.90	87	16	8	3	1,723	655	130	5.1	18.2	334	37	0.0
	D	84	4.27	94	13	4	3	1,705	573	137	5.9	12.5	328	30	1.9
G.H.	C	77	3.86	80	18	18	5	1,554	513	40	0.9	1.7	248	<19	0.0
	D	76	4.33	89	16	16	0	1,644	390	54	0.4	2.1	144	<19	1.4
T.C.	C	103	4.38	81	18	18	7	1,352	813	80	1.5	6.2	167	23	0.0
	D	94	5.59	93	16	16	0	1,331	461	55	0.1	5.8	60	21	1.8
D.L.	C	110	3.64	87	9	6	−6	2,044	1,097	149	1.5	2.5	123	30	0.0
	D	110	4.19	94	6	−2	−7	1,928	622	105	1.6	2.5	131	33	1.5
C.T.	C	101	2.80	91	25	23	5	2,457	658	<30	0.4	6.5	222	31	0.0
	D	81	4.17	84	14	12	−2	1,650	218	<30	0.5	2.3	112	34	1.3
R.C.	C	100	2.66	75	11	6	−1	2,286	651	130	2.5	8.3	293	<20	0.0
	D	97	2.74	76	8	4	−3	2,307	532	171	1.9	5.6	317	<20	2.6
H.L.	C	93	2.91	79	6	6	−2	2,227	938	129	9.3	3.2	298	<20	0.0
	D	84	2.91	82	5	5	−3	2,337	903	95	5.5	0.7	266	30	2.3
F.G.	C	97	3.40	75	17	16	−3	1,835	782	43	3.3	1.5	583	64	0.0
	D	83	3.36	77	10	9	−4	1,929	738	122	1.3	2.1	286	30	1.5
W.N.	C	82	2.72	75	10	2	0	2,205	489	154	2.1	0.5	299	34	0.0
	D	92	3.22	75	7	3	0	1,863	373	39	1.9	0.7	142	28	1.4
Mean	C	95	3.30	81	16	13	2	1,955	755	109	2.8	5.8	274	29	<0.03
±SEM		±3	±0.18	±2	±2	±2	±2	±100	±62	±19	±0.8	±1.5	±36	±4	
Mean	D	90	3.74	84	12	9	−1	1,881	544	101	1.9	4.6	208	26	1.7
±SEM		±3	±0.26	±2	±2	±2	±1	±89	±64	±15	±0.6	±1.4	±29	±2	±0.1
p Values		= 0.05	<0.02	<0.05	<0.001	<0.005	<0.01	NS	<0.001	NS	<0.02	NS	<0.05	NS	<0.001

Where individual hormone levels were below the limit of the assay, the lowest detectable concentration was used in calculating the mean.

ACTH = serum adrenocorticotropic hormone; ALDO = serum aldosterone; AVP = plasma arginine vasopressin; C = control; CO = cardiac output; D = 6 hours after digoxin infusion; DIG = serum digoxin; EPI = plasma epinephrine; HR = heart rate; NOR = plasma norepinephrine; NS = not significant; PAD = pulmonary arterial diastolic pressure; PRA = plasma renin activity; PWP = mean pulmonary wedge pressure; RA = mean right atrial pressure; SA = systemic arterial mean pressure; SEM = standard error of the mean; TSVR = total systemic vascular resistance.

TABLE III Hemodynamic and Hormonal Changes with Sitting Exercise

Pts.		HR (beats/min)	CO (liters/min)	SA (mm Hg)	PAD (mm Hg)	PWP (mm Hg)	RA (mm Hg)	TSVR (dynes s cm^{-5})	NOR (pg/ml)	EPI (pg/ml)	PRA (ng/ml/hr)	AVP (pg/ml)	ALDO (pg/ml)	ACTH (pg/ml)
W.B.	C	140	4.80	80	23	...	5	1,250	2,454	346	6.3	5.5	288	<19
	D	123	5.46	74	16	...	−2	1,114	1,304	265	4.3	10.8	400	<19
W.H.	C	104	5.43	96	38	30	24	1,061	1,406	181	0.7	12.6	264	<19
	D	103	5.65	105	35	27	16	1,260	1,258	233	0.2	6.4	264	<19
J.W.	C	110	6.33	105	22	13	6	1,251	813	127	7.2	18.8	240	34
	D	100	6.39	108	26	12	6	1,277	784	136	5.7	14.1	352	35
G.H.	C	98	4.48	98	22	...	11	1,554	1,706	119	1.6	...	...	...
	D	102	4.74	108	26	...	9	1,671	1,175	136	0.6	...	...	...
T.C.	C	116	5.81	85	24	...	19	909	1,083	128	12.8	6.9	230	27
	D	103	7.70	99	22	...	8	945	881	128	0.4	4.7	56	<19
D.L.	C	120	5.80	100	16	13	−2	1,407	1,530	246	3.4	1.9	146	34
	D	120	6.02	105	13	3	−2	1,422	1,356	192	2.1	1.4	146	33
C.T.	C	123	4.55	104	30	...	15	1,565	1,229	<30	0.5	4.7	252	34
	D	100	5.92	95	19	...	2	1,257	365	<30	0.5	0.9	126	34
R.C.	C	113	4.44	88	17	...	3	1,532	1,183	154	3.6	4.8	372	21
	D	104	5.24	90	14	...	−2	1,406	706	106	2.3	5.0	327	<20
H.L.	C	107	5.23	98	15	...	−2	1,530	2,893	174	11.1	10.2	348	40
	D	99	5.23	98	13	...	1	1,484	2,789	228	7.2	14.3	354	38
F.G.	C	111	3.93	87	30	23	5	1,669	...	...	...	...	...	...
	D	93	4.62	83	16	10	2	1,403	...	...	...	...	...	...
W.N.	C	123	4.81	98	34	23	3	1,580	...	...	...	...	...	...
	D	123	5.63	104	20	14	−1	1,492	...	...	...	...	...	...
Mean	C	115	5.06	95	25	20	8	1,392	1,589	167	5.2	8.2	268	29
±SEM		±3	±0.22	±2	±2	±3	±3	±73	±225	±30	±1.5	±1.9	±25	±3
Mean	D	106	5.69	97	20	13	3	1,339	1,180	162	2.6	7.2	253	27
±SEM		±3	±0.26	±3	±2	±4	±2	±60	±229	±25	±0.9	±1.9	±45	±3
p Values		<0.01	<0.005	NS	<0.05	<0.05	<0.02	NS	<0.02	NS	<0.005	NS	NS	NS

... = not done; other abbreviations as in Table II.

the increase in systemic arterial mean pressure during exercise, but there was no significant correlation at rest (Fig. 2).

Data on plasma arginine vasopressin and on serum aldosterone and ACTH were available in all 11 patients at rest and in 8 patients during exercise. Although arginine vasopressin tended to decrease both at rest and during exercise after digoxin was given, neither decrease was significant. Aldosterone declined 21% at rest, but was unchanged during exercise. ACTH was unaltered at both levels of activity. Plasma osmolality and plasma sodium and potassium concentrations averaged 279 mosm/kg, 134 mEq/liter, and 4.3 mEq/liter, respectively, at control rest, and remained constant with digoxin therapy.

Serum digoxin concentrations (Table II): The serum digoxin concentration was below the limits of the assay in all patients during the control period. Six hours after completion of the digoxin infusion, the serum digoxin level averaged 1.7 ± 0.1 ng/ml for the entire group of 11 patients. In the 8 patients with sequential digoxin determinations, the drug level was 6.6 ± 1.6 ng/ml at 1 hour and 1.7 ± 0.2 ng/ml at 6 hours after infusion ($p < 0.02$ for the difference between the 1-hour and 6-hour measurements).

Discussion

Total SVR is known to be elevated in patients with CHF, but the precise mechanisms of arteriolar constriction are not understood. Although structural abnormalities of the vessel wall may play an important role, there is also strong evidence for participation by a number of vasoactive neurohormonal systems. Plasma concentrations of norepinephrine are abnormally elevated in patients with CHF at rest[26–28] and during submaximal exercise,[26,29,30] and are presumed to reflect enhanced activity of the sympathetic nervous system.[31] The increases in plasma norepinephrine levels in the basal state are directly related to the severity of symptoms,[27] intracardiac filling pressures[26,28] and total SVR,[28] and are inversely proportional to the cardiac output.[26,28] PRA and arginine vasopressin levels are also elevated in many patients with heart failure,[22,23,28,32] although correlations between intracardiac pressures, total SVR and cardiac output on the one hand and these plasma hormones on the other have been poor in many series.[22,32]

Digitalis glycosides increase total SVR in normal persons[3,33] and constrict arterioles in the coronary,[33] skeletal muscle,[1,2,4,20] renal[20] and possibly mesenteric[20,34] beds. Several mechanisms have been implicated in the digitalis-induced vasoconstriction. The glycosides stimulate sympathetic outflow from the central nervous system,[35] promote release of endogenous catecholamines from terminals of adrenergic nerves,[36] prevent subsequent catecholamine reuptake,[37] and potentiate the reactivity of vascular smooth muscle to released norepinephrine.[38,39] In addition, digitalis has a direct vasoconstrictive effect that is inhibited by calcium-blocking agents.[2,38]

In contrast to the vasoconstrictive action uniformly observed in the normal circulation, the reported influence of digitalis glycosides on SVR in CHF in humans has been variable. Most studies, particularly those appearing before 1965, document a reduction in systemic resistance with digitalis.[4–12] In contrast, failure of resistance to decrease was noted as early as 1950 by Bayliss et al,[15] and this finding was confirmed 8 years later by Werko et al.[16] In a series of 15 patients with compensated CHF, Selzer and Malmborg[6] found no alteration in total systemic resistance with digoxin in a subset of 5 subjects who at baseline were clinically and hemodynamically indistinguishable from the 10 in whom resistance declined. Lack of reduction in SVR might have been expected in these studies, because in none did cardiac output or left ventricular filling pressures change significantly. However, subsequent investigations reported constancy of vascular resistance even in the face of clear enhancement of ventricular function.[17–19] Variability in the resistance responses to digitalis has been emphasized by Cohn et al,[40] who found that although resistance decreased in 4 of 8 patients with CHF, it actually increased in the other 4.

To some extent such conflicting results may relate to the definition of resistance—total systemic resistance vs total SVR—used by individual workers. However, differences in definition do not account for the observed discrepancies in the resistance response, because both

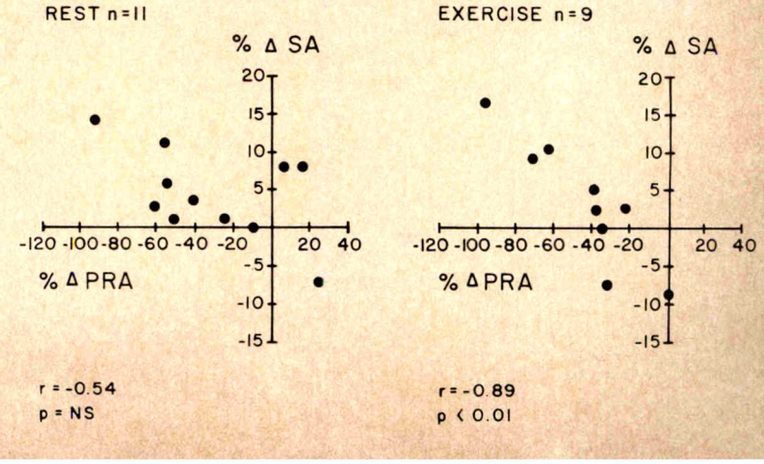

FIGURE 2. Correlations between percentage changes in systemic arterial mean pressure (% ΔSA) and in plasma renin activity (% ΔPRA) after digoxin therapy. NS = not significant.

calculated forms of resistance have been variously reported to either decrease or remain unchanged after digitalis. A partial explanation may be the heterogeneity in the causes and severity of CHF, as well as in cardiac rhythm, which has characterized most investigations to date. Thus, many series have included acutely ill patients or those with stenotic valvular disorders, cor pulmonale, uncontrolled hypertension or high-output states in addition to ischemic or cardiomyopathic disease. The timing of hemodynamic measurements may also affect the experimental observations. After the intravenous bolus administration of digoxin, both serum digoxin levels and tissue concentrations of the drug change rapidly,[41] and equilibrium is fully achieved only after 4 to 5 hours.[42] With a single exception,[18] all previous studies measured changes in vascular resistance less than 2 hours after infusion, when the serum digitalis concentration was expected to be far above the therapeutic range and the results were not necessarily indicative of the steady state.[40] No prior studies evaluating the acute changes in vascular resistance in patients with CHF have reported blood digitalis levels. In the present study, the serum digoxin concentration in 6 patients averaged 6.6 ng/ml at 1 hour after slow infusion of 1.0 mg of digoxin, in contrast to 1.7 ng/ml in the same patients 5 hours later.

To obviate these difficulties, the present protocol was designed to evaluate the short-term relation between cardiac pump function, vascular resistance and vasoactive hormones in a carefully defined group of patients with clinical and hemodynamic evidence of myocardial failure due to cardiomyopathy. Patients with atrial fibrillation, systemic hypertension, pulmonary disease, valvular disease or high-output states were specifically excluded. All subjects were clinically stable (although moderately disabled) at the time of hemodynamic intervention, and measurements were performed 6 hours after infusion. In addition, blood drawn simultaneously with the hemodynamic determinations was assayed for digoxin to assure the achievement of a therapeutic level.

Our observations support those of previous investigators, who found overall hemodynamic improvement with digitalis in patients with CHF. The mean increase in cardiac output 6 hours after digoxin infusion was statistically significant both at rest and during exercise, and was accompanied by decreases in left and right ventricular filling pressures. However, despite the substantial effects on ventricular function, total SVR did not decline significantly with digoxin either at rest or during exercise in this study. The resistance response was consistent: total SVR decreased by more than 10% in only 2 of 11 patients at both rest and during exercise. Improvement in cardiac index and filling pressures in patients with CHF with no change in total systemic resistance was first described with ouabain by Yankopoulos et al[17] in patients at supine rest. In a more recent paper, Murray et al[19] recorded no significant change in any hemodynamic variable with acute ouabain therapy in patients at sitting rest. Total systemic resistance was also unaltered during upright submaximal exercise, although cardiac output increased and left ventricular filling pressure decreased.[19] In the only previous investigation that evaluated hemodynamic effects more than 2 hours after drug infusion, Arnold et al[18] found an increase in cardiac index and a reduction in pulmonary wedge pressure, but no reduction in total systemic resistance with digoxin in patients at supine rest; however, a significant decline in total systemic resistance was demonstrated with maximal supine exercise. In the present study, no change occurred in total SVR at either rest or during submaximal exercise in patients in the sitting position.

Attempts to explain the vascular effects of digitalis in patients with CHF have focused on the known vasoactive neurohumoral systems, but a comprehensive hormonal-hemodynamic investigation has not yet been performed. The present investigation, therefore, sought to evaluate in a systematic manner the responses of the sympathetic nervous, renin-angiotensin-aldosterone and vasopressin systems to digoxin administration in the population with CHF, using blood hormone levels as indicators of neuroendocrine activity. Because both peripheral hormone concentrations[43] and vascular responsiveness[44] may be affected by dietary electrolyte intake or concomitant drug use, sodium and potassium ingestion was strictly controlled and all medications other than the study drug were eliminated. Smoking was discontinued and emotional stimuli were kept to a minimum in order to avoid raising plasma catecholamine concentrations.[45] In addition, catheterization was performed 1½ days before the study and all blood for hormone assays was drawn through the catheter (avoiding the trauma of multiple needle insertions).

Although total SVR did not change in these patients, plasma norepinephrine levels decreased consistently both at rest and during exercise, apparently confirming the postulated withdrawal of sympathetic tone. It is unlikely that the reduction in plasma norepinephrine levels merely reflects a diminution of the subject's anxiety as increased familiarity was gained with the experimental procedure, because control hormone levels were unchanged for at least 24 hours; norepinephrine is relatively insensitive to invasive procedures,[28] and the plasma levels of epinephrine—which have been taken as independent measures of psychic stress[28]—remained stable throughout. Reduction of plasma norepinephrine by digitalis may occur through several routes, including enhancement of norepinephrine uptake by postganglionic nerve terminals[46] and inhibition of norepinephrine synthesis.[35] Activation of high-pressure baroreflexes by a digitalis-induced increase in systemic arterial pressure results in the withdrawal of vasoconstrictive sympathetic discharge to blood vessels in skeletal muscle,[47,48] which can be prevented by carotid and aortic arch baroreceptor denervation[48] or ganglionic blockade.[47] No correlation was found in the present investigation between the decrease in plasma norepinephrine and changes in systemic arterial mean pressure. However, digitalis also sensitizes the arterial baroreceptor mechanism directly, even in the absence of significant increases in cardiac contractile force or arterial pressure.[49,50] In addition, the glycosides enhance the gain of a separate cardiopulmonary baroreflex with

vagal afferents, which induces vasodilation primarily in the renal bed.[51,52] Inhibition of catecholamine release from the adrenal gland[53] is unlikely to have played a significant role in our patients, because plasma epinephrine, the major catecholamine constituent of the adrenal medulla, did not vary with digitalis treatment.

In the present study, a significant correlation was documented between the reduction in plasma norepinephrine levels and the increase in cardiac output. This finding is consistent with the observation that plasma norepinephrine and cardiac output are inversely related in the CHF patient in the baseline state.[26,28] Accordingly, overall improvement in cardiac function owing to the inotropic action of digitalis may in itself lead to a reduction in sympathetic activity, although the mechanisms for this interaction must be determined.

In addition to the reduction in plasma norepinephrine concentrations, the present data revealed a decline in PRA in patients with CHF both at rest and during exercise after digoxin therapy. Similar results have recently been reported by Covit et al[21] in 6 patients with chronic CHF studied at rest. In that report, the percentage reduction in PRA was comparable to the one observed in this study and the nadir of PRA was noted when serum digoxin concentrations were approximately 2 ng/ml. Covit et al[21] also described a decrease in the serum aldosterone concentration, which was confirmed by the current study. Unfortunately, simultaneous hemodynamic measurements were not performed.

In the present investigation, the decrease in PRA with digoxin may have had several origins. The highly significant correlation observed with exercise between the increase in systemic arterial mean pressure and the reduction in PRA is consistent with the inhibitory effect of elevated renal perfusion pressure on renin release,[54] although this relation could not be demonstrated in patients at rest. In addition, the glycoside may have sensitized the cardiopulmonary baroreflex with vagal afferents, augmenting its suppressive effects on renal sympathetic nerve activity and, thus, on renin release.[51,52,55] The possibility also exists that digoxin inhibited renin secretion by a direct effect on the renal cortex as has been shown in both in vitro[56] and in vivo[57] preparations. Among the humoral agents and electrolytes known to promote release of renin,[54] plasma epinephrine, arginine vasopressin, ACTH, sodium and potassium levels did not change in this study and thus probably did not contribute to the decline in PRA; however, local intrarenal effects cannot be excluded with certainty.

Norepinephrine and PRA levels decreased in this study despite the reductions in cardiac filling pressures, which are normally associated with increased levels of these hormones.[58,59] On the contrary, the decrease in plasma norepinephrine concentration correlated positively with the decline in right atrial pressure.

In the dog, release of vasopressin, like PRA, is inhibited by cardiopulmonary reflexes with vagal afferents.[60] However, digoxin in normal conscious dogs does not detectably suppress plasma arginine vasopressin, even when basal hormone levels are elevated by water restriction.[61] Moreover, vasopressin concentrations in normal human subjects are not affected by loading of cardiopulmonary or sinoaortic baroreceptors.[62] Responses of vasopressin to digitalis therapy in patients with CHF have not previously been reported. In the present study, neither arginine vasopressin nor plasma osmolality changed significantly after digoxin.

It is interesting that total SVR did not decrease in our patients despite significant reductions in PRA and plasma norepinephrine levels. The PRA findings appear to be consistent with those of previous investigations showing a poor correlation between PRA and hemodynamic variables in patients with CHF.[28,32] The norepinephrine result was unexpected, however, given the reported correlation between plasma norepinephrine levels and total SVR in patients in the baseline state.[28] In this study, the vasodilation anticipated from reduced plasma norepinephrine levels may have been blocked by the constrictive action of the digoxin itself. On the other hand, alternative mechanisms are suggested by the study of Schwartz et al,[63] who found no change in vascular resistance in patients with CHF when plasma norepinephrine levels were lowered by direct pharmacologic inhibition of catecholamine synthesis. Failure of resistance to decline in both experimental situations might be explained either by inability of the arterioles in patients with CHF to dilate normally in response to withdrawal of sympathetic tone (as has been shown with a variety of vasodilator stimuli[64]) or by the existence of other influences (possibly neurohumoral in nature) which exert a constrictive effect equal in magnitude to the potential vasodilation. Candidates for the latter role include reductions in the vasoactive kinins[65] or alterations in prostaglandins,[66] but these possibilities have not been evaluated.

In this study, cardiac output increased even though total SVR remained constant and both heart rate and pulmonary wedge pressure decreased. Accordingly, digoxin appears to have had a potent inotropic effect in these patients with CHF. This conclusion is strengthened by the observation that plasma norepinephrine levels declined, since sympathetic inhibition can be presumed to, if anything, further erode the strength of contraction of the failing myocardium. In studies reporting a decrease in SVR in patients taking digitalis, augmentation of cardiac output has been, in all cases, greater than that recorded here. However, it is unclear whether such increases are mainly the result of the direct effect of digitalis on the heart or of afterload reduction due to reflex-dilating actions on the peripheral vasculature. Because total SVR did not decline in the present investigation, the improvement in ventricular function with digoxin that we observed appears to have been entirely a result of enhancement of myocardial contractility.

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Response to the Valsalva Maneuver After the Fontan Procedure for Tricuspid Valve Atresia, Single Ventricle or Pulmonic Valve Atresia

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The Valsalva maneuver was performed during cardiac catheterization in 9 patients who had undergone a Fontan operation (Fontan group) and in 10 control subjects. The Fontan group had higher right atrial (RA) pressure (16 ± 1 vs 4 ± 0.5 mm Hg, p <0.001), lower cardiac index (2.5 ± 0.1 vs 3.7 ± 0.2 liters/min/m^2, p <0.05), lower stroke index (32 ± 2 vs 44 ± 2 ml/beat/m^2, p <0.05), and higher systemic vascular resistance (31 ± 1 vs 24 ± 1 units, p <0.05) than the control group. Four patients in the Fontan group had a normal 4-phase Valsalva response, and 5 did not (p <0.05). RA pressure was similar in those who responded normally and those who did not (16 ± 0.5 vs 17 ± 1 mm Hg), whereas in those who responded normally cardiac index was higher (2.9 ± 0.2 vs 2.2 ± 0.1 liters/min/m^2, p <0.05), stroke index was higher (36 ± 1 vs 28 ± 1 ml/beat/m^2, p <0.05), and systemic vascular resistance was lower (28 ± 1 vs 31 ± 1, p <0.05). It is concluded that cardiac output is a better predictor of a normal response to the Valsalva maneuver than RA pressure in patients after the Fontan procedure. A normal response to the supine Valsalva maneuver suggests a cardiac index greater than 2.4 liters/min/m^2 and stroke index greater than 31 ml/beat/m^2. (Am J Cardiol 1985;56:905–909)

The Valsalva maneuver—maximal expiration against a closed glottis—is considered an excellent physiologic test for congestive heart failure.[1–4] During the maneuver, systemic venous return is obstructed, cardiac output decreases, and a reflex increase in systemic vascular resistance and heart rate occur. After release of strain, cardiac output increases and a characteristic overshoot in aortic pressure and pulse pressure occurs, as does reflex bradycardia. In patients with congestive heart failure, systemic venous return is not effectively diminished and a "square-wave response" with absence of the overshoot is observed (Fig. 1).

Elevated right atrial (RA) pressure and low cardiac output have been associated with an abnormal response to the maneuver.[1–3,5,6] Patients who have undergone the Fontan operation for repair of congenital heart disease (direct RA-to-pulmonary trunk or RA-to-right ventricle communications) usually have elevated RA pressure or low cardiac index as sequelae of the operation.[7–10] We performed the Valsalva maneuver in patients who had undergone successful repair by Fontan operation to determine if a normal aortic pressure response to the Valsalva maneuver is present, and if so, whether the patient's RA pressure or cardiac output are a better determinant of the normal response.

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Methods

The Valsalva maneuver was performed in 19 patients during routine diagnostic cardiac catheterization. A Fontan or modified Fontan operation was performed in 9 patients (6 for tricuspid atresia, 2 for single ventricle and 1 for pulmonary atresia with intact ventricular septum). Ten patients served as control subjects. Mild congenital heart disease was present in 5 (mild aortic stenosis in 2 and mild pulmonic stenosis, mitral valve prolapse and cervical aortic arch in 1 patient each) and 5 were undergoing electrophysiologic study for localization of an accessory bypass tract. The mean age of patients with a Fontan operation was 15 ± 2 years and that of control subjects was 15 ± 1 years. The mean interval between operation and cardiac catheterization in the Fontan group was 3 ± 1 years. The operation performed was RA-to-pulmonary artery anastomosis in 7 patients, RA to right ventricular anastomosis in 1 patient and RA to pulmonary artery valved

TABLE I Hemodynamic Values at Rest in the Fontan Group and the Control Group

	Fontan Group (n = 9)	Control Group (n = 10)	p Value
Change in PAP, end strain (phase II to phase III) (mm Hg)	46 ± 7.0	36 ± 4.0	NS
Mean RAP (mm Hg)	16 ± 1	4 ± 0.5	<0.001
Cardiac index (liters/min/m^2)	2.5 ± 0.1	3.7 ± 0.2	<0.05
Stroke index (ml/beat/m^2)	32 ± 2	44 ± 2	<0.05
SVR (Wood units)	31 ± 1	24 ± 1	<0.05

NS = not significant; PAP = pulmonary artery pressure; RAP = right atrial pressure; SVR = systemic vascular resistance.

conduit in 1. This latter conduit was stenotic (15-mm Hg mean gradient) at the time of catheterization. In the Fontan group, 3 patients were in New York Heart Association (NYHA) functional classification class I, 3 were in class II and 3 were in class III. All control patients were class I.

All patients were supine. In each patient resting values of heart rate (average of 3 RR intervals), aortic pressure, RA pressure, pulmonary artery pressure and left ventricular end-diastolic pressure were simultaneously measured. Cardiac output was determined by thermodilution and indexed to body surface area. Stroke index and systemic vascular resistance were calculated. In 7 patients in the Fontan group left ventricular ejection fraction was determined from the left ventricular cineangiograms using Simpson's rule.

To perform the Valsalva maneuver each patient was asked to place his thumb in his mouth and expire maximally without allowing any air to escape. The maneuver was sustained until the characteristic rise and plateau in aortic diastolic pressure was observed, indicating an increase in peripheral resistance. Total duration of effort was between 10 and 15 seconds. Heart rate, aortic pressure and pulmonary artery pressure were recorded throughout the effort and for 20 cardiac cycles thereafter. Effort was assessed by measuring the decline in pulmonary artery systolic pressure (or a-wave) at the release of strain. This decrease was considered to reflect transthoracic pressure induced by the strain since there is no significant change in cardiac output at the transition from end strain (phase II) to release (phase III).[11,12] A difference of more than 20 mm Hg indicated a satisfactory effort (Table I). The response to the Valsalva maneuver was quantitated by assessing changes in aortic systolic pressure, aortic pulse pressure and heart rate during the maneuver (Fig. 2). For each variable, the difference from values at rest was determined at the release of strain (phase III) and at the peak pulse pressure during the overshoot (phase IV). The number of beats from release of the strain to peak pulse pressure was calculated for each patient with a normal response curve. A normal response curve was defined as having all 4 phases of the characteristic response present for each variable (systolic pressure, pulse pressure and heart rate). All other responses were classified as abnormal.

Within each group, mean and standard error of the mean were calculated for each variable at rest. The Fontan group was further subdivided into normal and abnormal responders. Group comparisons were made using the unpaired t test. A level of 0.05 was selected as the criterion for significance of a positive result.

Results

Hemodynamic values measured at rest are presented in Table I. The Fontan group has significantly higher mean RA pressure, lower cardiac index, lower stroke index and higher systemic vascular resistance than the control group. Systolic blood pressure at rest (114 ± 3

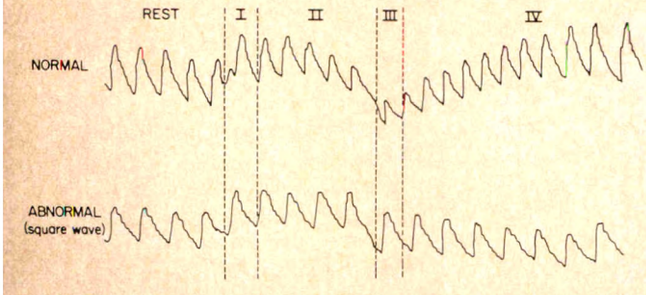

FIGURE 1. Normal and abnormal aortic pressure responses to the Valsalva maneuver in patients after Fontan operation. Phase I represents the onset of strain. Phase II, which has been shortened, represents the maintenance of strain. Phase III is the release of the strain. Phase IV is referred to as the overshoot period. In the normal response during phase I, there is an immediate increase in systolic blood pressure, corresponding to the increase in transthoracic pressure. In phase II, systemic venous return is obstructed by the increased transthoracic pressure. As a result, systolic blood pressure and pulse pressure fall. Heart rate and systemic resistance increase as cardiac output decreases. During phase III, systolic pressure decreases well below values at rest, reflecting the decrease in transthoracic pressure and cardiac output. Pulse pressure remains low and tachycardia persists. In phase IV, systemic venous return and cardiac output rapidly increase, causing an increase in systolic pressure and pulse pressure. These pressures increase above values at rest because of the increased systemic resistance and produce a reflex bradycardia. In the patient with congestive heart failure, the obstruction to venous return does not alter cardiac performance. Therefore, pulse pressure and heart rate remain constant during phase II, and return to baseline values at end strain, giving the characteristic "square-wave" appearance to the response curve.

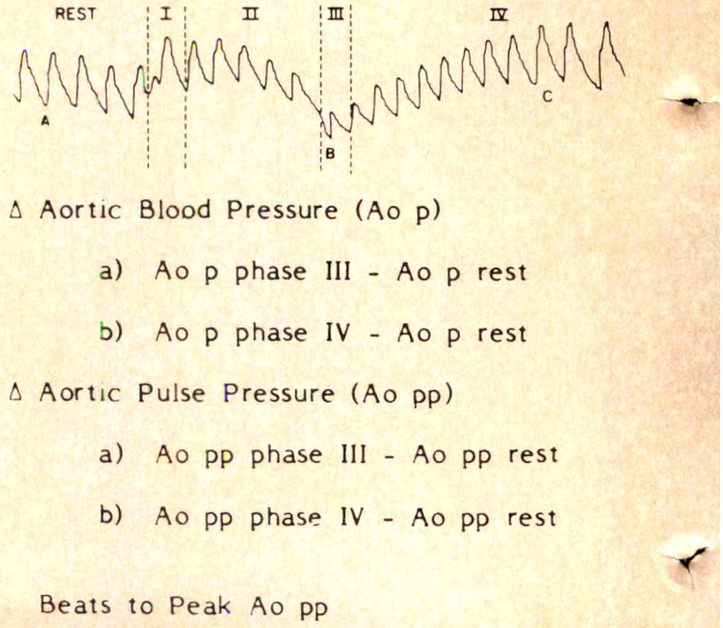

FIGURE 2. Calculation used to quantitate the shape of the Valsalva response curve. **A, B** and **C** demonstrate the beats selected to make measurements of systolic pressure, pulse pressure and beats to peak pulse pressure respectively. Heart rate was calculated as the average of 3 RR intervals before strain, at phase III, and during reflex bradycardia.

vs 119 ± 3 mm Hg), pulse pressure (34 ± 3 vs 37 ± 2 mm Hg) and heart rate (78 ± 5 vs 86 ± 4 beats/min) were similar in both groups. Whereas all 10 control patients had a normal 4-phase response to the maneuver, 4 Fontan patients had a normal response and 5 had an abnormal response (Fig. 3). At end strain (phase III), patients in both control and Fontan groups with a normal response had a similar decrease in systolic pressure (40 ± 5 vs 37 ± 9 mm Hg), decrease in pulse pressure (18 ± 2 vs 25 ± 4 mm Hg), and increase in heart rate (29 ± 4 vs 20 ± 4 beats/min) (differences not significant [NS]). During the overshoot (phase IV) these groups had similar (NS) increases in systolic pressure (27 ± 4 vs 30 ± 4 mm Hg), and pulse pressure (17 ± 3 vs 20 ± 2 mm Hg); reflex bradycardia (−21 ± 3 vs −21 ± 4 beats/min). However, the number of beats to peak pulse pressure during the overshoot was significantly lower in the control group (9 ± 1 vs 12 ± 1 beats, $p < 0.05$), suggesting delayed transmission of the systemic venous return to the left heart in the Fontan group.

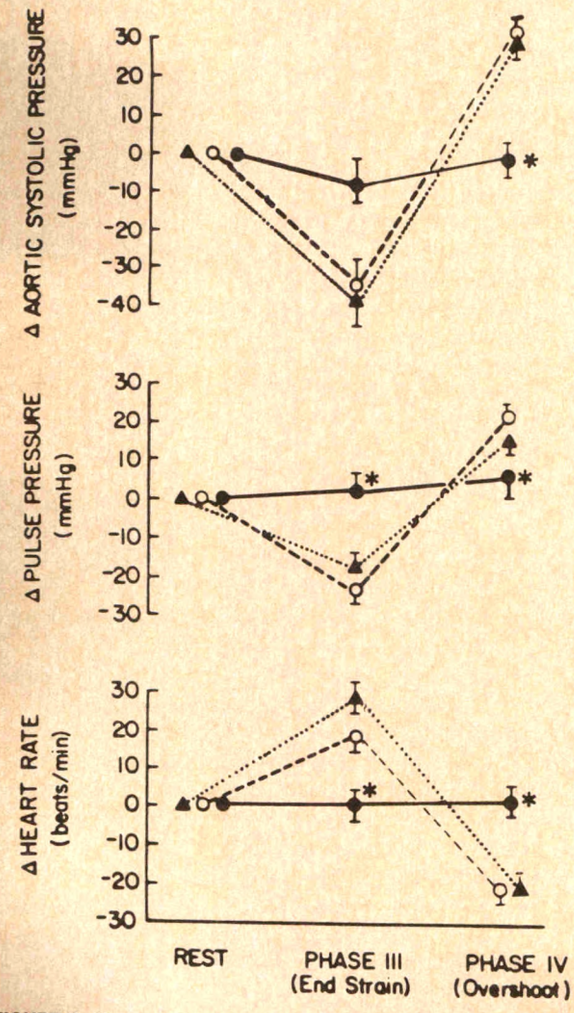

FIGURE 3. Change from values in response to the Valsalva maneuver in 3 groups: control patients (**triangles**), Fontan patients with a normal qualitative response (**circles**) and Fontan patients with an abnormal response (**dots**). Statistical differences (*$p < 0.05$, Fontan abnormal response group vs control group) were found between the control group and the group with an abnormal response in aortic systolic pressure, pulse pressure and heart rate at end strain and during the overshoot.

The 5 patients in the Fontan group with an abnormal Valsalva response had no significant change from rest values to the release of strain or during the overshoot in systolic pressure (−6 ± 8 mm Hg, end strain; −2 ± 4 mm Hg, overshoot), pulse pressure (1 ± 6 mm Hg, end strain; 5 ± 2 mm Hg, overshoot), or heart rate (2 ± 3 beats/min, end strain; 3 ± 2 beats/min, overshoot). Compared with patients in the control group, patients in the Fontan group with an abnormal response had statistically different systolic pressure, pulse pressure and heart rate responses at end strain and during the overshoot (Fig. 3).

Figure 4 is a comparison of RA pressure, cardiac index, stroke index and systemic vascular resistance between the 2 Fontan groups. RA pressure did not differ significantly between the 2 groups (16 ± 0.5 vs 17 ± 1 mm Hg); however, those with a normal response had a higher mean cardiac index (2.9 ± 0.2 vs 2.2 ± 0.1 liters/min/m^2, $p < 0.05$) and higher stroke index (36 ± 1 vs 28 ± 1 ml/beat/m^2, $p < 0.05$). A cardiac index of 2.4 liters/min/m^2 or less and a stroke index less than 31 ml/beat/m^2 were associated with an abnormal Valsalva response. Systemic vascular resistance was also significantly lower in the normal response group (28 ± 1 vs 31 ± 1 units, $p < 0.05$). In both groups mean left ventricular end-diastolic pressure was 8 ± 1 mm Hg. Among the 7 patients with Fontan operation in whom an ejection fraction was measured, the 3 patients with the highest ejection fractions (70%, 76% and 78%) had a normal response to Valsalva maneuver and 4 (range 31 to 61%) had an abnormal response. Three of the 4 patients with a normal response were in NYHA functional classification I and 1 patient was in class II. All patients who

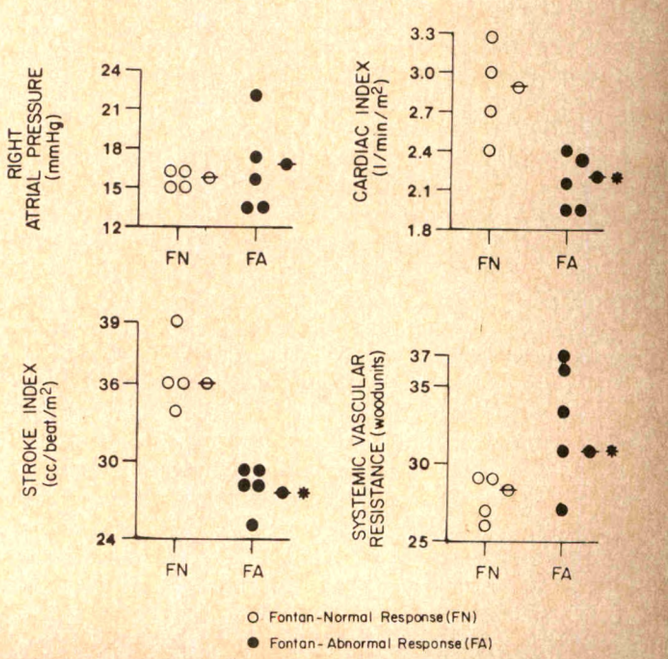

FIGURE 4. Hemodynamic measurements at rest in Fontan patients with a normal response to the Valsalva maneuver (**circles**) and those with an abnormal response (**dots**). **Crossed symbols** represent mean values. Right atrial pressure was similar in both groups. However, cardiac index and stroke index were statistically higher and systemic vascular resistance was lower (*$p < 0.05$) in the normal response group.

responded abnormally were in functional class II or greater. Thus, in our patients who have undergone a Fontan operation, response to the Valsalva maneuver is independent of RA pressure and appears to be related to cardiac performance as reflected by assessment of cardiac output, stroke volume, ejection fraction and NYHA functional classification.

Discussion

The Valsalva maneuver initiates a complex sequence of hemodynamic and reflex responses in the normal[13] subject (Fig. 1) and fails to initiate this sequence in the patient with congestive heart failure because systemic venous return is not sufficiently obstructed during the maneuver.[3,5,11,12] The characteristic fall in systolic pressure and pulse pressure below baseline at the release of strain, subsequent overshoot of systolic pressure and pulse pressure, and reflex heart rate responses are absent in the latter group. Several studies indicate that elevated RA pressure and right ventricular dysfunction cause an abnormal response to the Valsalva maneuver. An abnormal response has been found in patients with right ventricular failure secondary to cor pulmonale or pulmonic stenosis.[1–3] Judson et al[2] correlated the presence of an abnormal response with elevation of right ventricular end-diastolic pressure and speculated that patients with left-sided heart failure or left-sided obstruction would not develop an abnormal response unless elevations of right ventricular end-diastolic pressure were also present. By producing an acute volume load in patients with a normal response and thus increasing RA pressure, Judson changed the response to a "square wave." Conversely, maneuvers that diminished RA pressure, such as venesection or the placement of thigh cuffs altered abnormal responses to normal. O'Neill and Cudkowicz[6] studied patients with normal and abnormal responses to Valsalva maneuver and demonstrated elevated RA pressures (mean 16 mm Hg) in patients with an abnormal response. Wilkinson et al[5] performed Valsalva-like maneuvers in anesthetized dogs and studied the effects of changes in blood volume and RA pressure. They concluded that an abnormal response could be induced by increasing central blood volume. Elevation of RA pressure produced by the increased blood volume increased effective RA pressure (RA pressure − transthoracic pressure), prevented obstruction of venous return, and thus caused an abnormal response to the maneuver.

Because patients who have undergone a Fontan operation have elevated RA pressures[7–10,14–16] and either lack or have a poorly functioning right ventricular pump, the above clinical and experimental studies would suggest that patients should have an abnormal response to the Valsalva maneuver after they undergo the Fontan procedure. Why, then, did 4 of our 9 patients have a normal response? The data suggest that the most important determinant is left ventricular performance. The Fontan operation establishes an essentially passive channel between the systemic venous return and the pulmonary circulation. Pulmonary flow and RA pressure are, in large measure, dependent on left ventricular end-diastolic pressure, resistance of the pulmonary circulation and resistance of the conduit. RA pressure under these circumstances is expected to be elevated because it will reflect the total resistance to flow. Our patients with elevated RA pressure but higher cardiac index, stroke index, and left ventricular ejection fraction had normal responses to the Valsalva maneuver. We postulate that in those patients, the left ventricle drains the pulmonary vasculature during the strain. Effective RA pressure is sufficiently low to obstruct venous return and remains low because of an effective left ventricular pump. When strain is released, the dammed venous return is transmitted to the left side of the heart, producing overshoot. Patients with low cardiac index because of left ventricular dysfunction will not have low effective RA pressures at the onset of strain and will not effectively drain their pulmonary circulation during the strain. Systemic venous return will not be occluded and cardiac output will remain unchanged, thus producing a "square-wave response."

Patients with right ventricular failure secondary to cor pulmonale or pulmonic stenosis have elevated RA pressures because of obstruction to pulmonary flow, poor right ventricular compliance and increased blood volume in the venous capacitance vessels.[17] These factors contribute to maintaining a higher effective RA pressure during the Valsalva strain, failure to diminish venous return, and the subsequent abnormal response.[2,5] Indeed, in 1 of our patients with an obstructed conduit, obstruction contributed to a low cardiac index and an abnormal Valsalva response.

Patients who responded abnormally after the Fontan operation had poorer cardiac function as assessed by cardiac index, stroke index and ejection fraction, but their left ventricular end-diastolic pressures were similar to those of the patients who responded normally and were within the normal range of values. This similar left ventricular end-diastolic pressure value accounts for the similarity in RA pressure between groups (the only exception being that patient with an obstructed valved conduit and RA pressure of 22 mm Hg). The explanation for the similarity in pressures, despite marked differences in measured overall cardiac performance, may relate to the difference in the determinants of left ventricular preload in Fontan patients compared with patients with structurally normal hearts. In the structurally normal heart, left ventricular failure results in pulmonary congestion, elevation of pulmonary venous pressure and, when severe, right ventricular failure. In patients who have undergone the Fontan operation, and have direct RA to pulmonary artery continuity, there is no pulmonary valve and no effective right ventricular pump. When the left ventricle fails, it has not only the pulmonary circulation, but the whole venous capacitance as a reservoir. Thus, a much larger increase in blood volume may be necessary to increase left ventricular end-diastolic pressure in patients who undergo the Fontan procedure.[18]

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LETTERS*

VENTRICULAR REMODELING IN MYOCARDIAL INFARCTION—THE RAT AND THE HUMAN

The excellent analysis by Roberts et al[1] of left ventricular (LV) remodeling in a rat infarct model makes several observations that should be related to LV remodeling in the human after acute myocardial infarction. Infarct expansion is defined as stretching and thinning of the infarct zone after AMI and it leads to LV dilatation and distortion.[2] Data of Roberts et al[3] show that any increase in LV cavity size in the rat 2 days after AMI is due to tissue resorption in the infarct zone, inasmuch as there is no increase in the outer LV dimensions at that time; i.e. there is no increase in infarct segment length. In contrast, our 2-D echocardiographic (echo) studies in humans have shown dramatic increases of infarct segment length up to twice normal within the first 24 hours and as soon as 90 minutes of the onset of chest discomfort, before inflammation or tissue resorption has begun.[4] In humans, marked increases in radiographic cardiac sillhouette size in the early hours of AMI also speak for an increase in external heart size, which in our 2-D echo studies is primarily due to infarct expansion rather than the Starling effect.[4,5]

Infarct zone scar contraction over several weeks in the infarct segment, reported in the study of Roberts et al, is consistent with similar findings by Theroux et al[6] in the canine infarct model. We observed a similar tendency in the infarct zone in our long-term 2-D echo studies of infarct patients, but only in those *without* infarct expansion.[7] In patients *with* infarct expansion, the infarct segment tended to *increase* in length over a mean 13-month follow-up. "Compensatory" lengthening of the noninfarcted segment over 3 weeks was seen in Roberts' study, an observation we also made in patients with infarct expansion in long-term follow-up.[7]

The data in this article also show the independence of LV wall thinning and infarct expansion, terms that have sometimes been used interchangeably. These 2 phenomena are functionally related to each other only in the first hours of AMI, when stretching of myocardium necessarily leads to a decrease in wall thickness. However, the tissue resorption and scar replacement of necrotic myocardium come under the influence of the multifactorial processes of healing, which may well lead to variability of wall thickness independent of the degree or even the presence of infarct expansion as shown in this study.

In summary, there appear to be major differences in the topographic behavior of the rat heart after AMI compared to the human. Although studies such as this help to focus attention on the importance of infarct-associated topographic changes, they point out that models more closely mimicking the human infarct are needed.

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31 August 1984

1. **Roberts CS, Maclean D, Maroko P, Kloner RA.** Early and late remodeling of the left ventricle after acute myocardial infarction. Am J Cardiol 1984;54:407–410.
2. **Hutchins GM, Bulkley BH.** Infarct expansion versus extension: two different complications of acute myocardial infarction. Am J Cardiol 1978;41:1127–1132.
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SYSTOLIC TIME INTERVALS IN CORONARY HEART DISEASE AT REST AND DURING EXERCISE

Vanhees et al[1] present interesting and practical conclusions on the effect of β-adrenoceptor blockade on physical training and exercise. I was surprised, however, at some important details of the protocol as published. I have no quarrel with their conclusions regarding the effect of β-adrenoceptor blockade. Can they clarify the following: (1) It appears that all 28 patients both achieved exercise at 110 W and had adequate recording of systolic time intervals (STI) by ordinary methods (i.e., methods virtually immune to motion artifact like the ear densitogram[2] were not used). They do not specify whether a funnel, a balloon or a pressure sensitive device was positioned over the carotid artery. With these "standard" pickups, it is common, as with PCG microphones, for many exercising patients to produce considerable artifact.[3] It is thus surprising that satisfactory data could be obtained from all 28 patients. (2) The investigators analyzed only 3 consecutive beats (usually 10 or even 5 consecutive beats are averaged for STI). Perhaps this was because of technical beat-to-beat variation due to motion artifacts, but this would not permit averaging over the respiratory phases, and respiratory effects during exercise are exaggerated. Were the patients recorded during voluntary apnea? (3) The preejection period (PEP) is described as significantly affected by heart rate (HR). However, it has been shown repeatedly[4] that direct HR effect is unlikely, and that PEP and HR are individually under the influence of sympathetic tone at rest and sympathetic stimulation during exercise. They further indicate that they used PEPc, because they were attempting to allow for HR[4]. They discuss "PEPc" referring to Table VI. However, Table VI mentions PEP, not PEPc in its title. If this, in fact, is PEPc, it would be possible to extract PEP by considering the HR. For example, a rough estimation from Figure 1 for HR at 110 W gives the following approximate HR: no β blockade—before training, 131 beats/min; after training, 111 beats/min; with β blockade—before training, 112 beats/min; after training, 103 beats/min. If we then arbitrarily apply Weissler's slope factor for PEP vs HR, 0.4, we can recalculate the uncorrected PEP as 48, 28, 33 and 47 ms, respectively. (These will be wrong if Vanhees et al used a different "correction"—but directionally correct). These PEP results indicate much greater relative changes than are shown in the table and may be highly significant for the difference between treatment groups. The text is unclear as to whether Table VI is really PEP or PEPc. Furthermore, in any article on STI the actual HR at every point should be given.

These comments are made not so much in direct criticism of an otherwise excellent work, but rather in search of clarification.

David H. Spodick, MD
Worcester, Massachusetts
10 September 1984

1. **Vanhees L, Fagard R, Grauwels R, Wijnhoven J, De-Geest H, Amery A.** Systolic time intervals in coronary heart disease at rest and during exercise: effect of physician training with and without beta blockade. Am J Cardiol 1984;54:508–513.
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REPLY: In response to the letter of Spodick, the following may clarify the various problems raised: (1) The carotid pulse was obtained by a funnel device (pulse transducer Siemens 860-2). During exercise it was attempted to position the device so that adequate recordings were obtained, which, at the pretraining evaluation, was successful in 39 patients. Of these, 11 were lost to study for problems not related to methodology. We failed, however, to register adequate pretraining data at exercise in 9 other patients, who were therefore excluded from further study. (2) The recordings were made at end-expiration during brief periods of voluntary apnea, both before and after training. We agree that adequate recordings would not be possible at exercise throughout respiration. The variation in 3 consecutive beats recorded in held respiration during exercise is sufficiently small so that the average of 3 beats is adequate. (3) For comparison of STI before and after training, analysis of covariance was applied. For PEP at rest in the recumbent

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position, HR was not a significant covariate, which is in agreement with the data of Spodick and others. At exercise, however, HR was a significant covariate for PEP, so that the correction of PEP for HR was considered mandatory. (4) All reported STI in tables and figures are measured STI. The statistical comparisons were made on the basis of analysis of covariance; since HR was a significant covariate for left ventricular ejection time (LVET) and PEP during exercise, the F values for the effect of training are based on $LVET_c$ and PEP_c (i.e. taking HR into account).

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Robert Fagard, MD
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19 October 1984

BALLOON DILATATION CATHETER SIZE SELECTION

I read the recently published Proceedings of the National Heart, Lung, and Blood Institute (NHLBI) Workshop on the Outcome of Percutaneous Transluminal Coronary Angioplasty (PTCA).[1] In that review, Cowley et al reported that coronary arterial dissection is more frequent in women, in dilatations of the right coronary artery, in patients with more advanced multivessel disease, or in vessels with tubular, nondiscrete or eccentric lesions.[2] I question whether some of these may not have been patients in whom coronary diameter was smaller. I am writing in hopes of stimulating more discussion of the choice of balloon dilatation catheter size. Previous experience in our laboratory was patterned after that reported by Gruentzig and Meier[3] in the same workshop with "almost all" cases being done with 3.0-mm outer diameter balloon catheters and 2.0-, 2.5- and 3.7-mm sizes being used for special situations only. More recently, however, I have considered that coronary dissection should be more frequent if overdilatation is performed. Consequently, I have recently been trying to match more objectively the balloon catheter size to the desired lumen diameter. This was first done using measurements from calibrated 105-mm films and a 5-inch image intensifier. Equally accurate selections can be made, however, simply by comparison of desired lumen size to the diameter of arteriographic catheters on cineangiograms. The 1/3-mm and French size relation is useful to remember: *French size:* 6, 7.5, 8, 9, 10.5, 11.1; *diameter in mm:* 2.0, 2.5, 2.67, 3.0, 3.5, 3.7. If this were used in selecting a dilatation catheter, the 3.0-mm balloon would be chosen when the desired arterial diameter was equal to the diameter of a 9Fr guiding catheter.

I suspect that established investigators (such as those who participated in the NHLBI Workshop), from experience, can make the catheter selection accurately without such a formal comparison. Angiographers who perform angioplasty less often may find it helpful. I would appreciate the comments of other investigators as to whether they believe individualization of the balloon size is likely to be helpful. In addition, it would be interesting if one of the major centers performing angioplasty would conduct a retrospective review in which balloon dilatation catheter size was converted to a percentage of optimal arterial luminal diameter. A comparison of a group of patients with long-term good result, a group with restenosis, and a group with arterial dissection may be able to establish whether relative balloon size is a factor in either dissection or restenosis.

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Pensacola, Florida
11 September 1984

1. **Kent KM, Mullin SM, Passamani ER.** Proceedings of the National Heart, Lung, and Blood Institute Workshop on the Outcome of Percutaneous Transluminal Coronary Angioplasty. Am J Cardiol 1984;53:1C–146C.
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3. **Gruentzig AR, Meier B.** Current status of dilatation catheters and guiding systems. Am J Cardiol 1984;53:92C–93C.

REPLY: The selection of balloon dilatation catheters to more closely approximate the size of smaller arteries may reduce the risk of coronary dissection but may also have an adverse effect on lesion recurrence rates. Data from this institution,[1,2] however, suggest that coronary dissection is largely a function of lesion morphology and agrees with the findings of the NHLBI Registry (Ref. 2 above).

Higher inflation pressure, which in part influences balloon diameter, is a major determinant of expansile stress within the artery. A modest increase in balloon inflation pressure does not increase the incidence of acute complications or dissection but improves the immediate haemodynamic results and may have had a favorable effect on lesion recurrence.[3] More recent data confirmed the importance of a satisfactory final transstenotic gradient in reducing the recurrence rate.[4,5] Whether this is best achieved by longer balloon inflations, higher inflation pressures or larger balloon sizes is unknown.

Preliminary reports from other centers have suggested that a larger balloon diameter/arterial diameter ratio does not increase the risk of dissection[6,7] but may significantly reduce recurrence rate.[7] We are currently undertaking a study examining the influence of balloon size on acute complication and recurrence rates. However, more severe degrees of intimal dissection are certainly associated with increased risk of acute closure and emergency coronary surgery.[8] Until definitive results are available, it would be prudent to carefully match balloon size to arterial lumen diameter, remaining on the smaller side of the scale. Our approach has been to do this by referring to the known diameter of the 8Fr or 9Fr guiding catheters. In practice this usually results in choosing a 3.0-mm balloon while occasionally using balloons of 2.5 mm or 3.7 mm in diameter (Ref. 1 above).

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Pierre P. Leimgruber, MD
Andreas R. Gruentzig, MD
Atlanta, Georgia
3 December 1984

1. **Meier B, Gruentzig A, Hollman J, Ischinger T, Bradford J.** Does length or eccentricity of coronary stenoses influence the outcome of transluminal dilatation? Circulation 1983;67:III:III–479–III–499.
2. **Hall DP, Gruentzig AR.** Influence of lesion length on initial success and recurrence rates in coronary angioplasty (abstr). Circulation 1984;70:suppl II:II–107.
3. **Meier B, Gruentzig AR, King SB, Douglas JS, Hollman J, Ischinger T, Galan K.** Higher balloon dilatation pressure in coronary angioplasty. Am Heart J 1984;107(4):619–622.
4. **Leimgruber PP, Roubin GS, Rice CR, Tate JM, Gruentzig AR.** Influence of intimal dissection after coronary angioplasty (PTCA) on restenosis rate (abstr). Circulation 1984;70:suppl II:II–175.
5. **Holmes DR, Vlietstra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, Faxon DP, Gruentzig AR, Kelsey SF, Detre KM, Van Raden MJ, Mock MB.** Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1984;53:77C–81C.
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7. **Schmitz HJ, von Essen R, Meyer J, Effert S.** The role of balloon size for acute and late angiographic results in coronary angioplasty (abstr). Circulation 1984;70:suppl II:II–295.
8. **Leimgruber PP, Roubin GS, Bredlau C, Gruentzig AR.** The influence of coronary artery dissection on the initial and long term success of PTCA. In press.

REPLY: Rogers' questions and comments regarding dilatation catheter size selection are useful. Concerning factors associated with a higher frequency of dissection in the NHLBI PTCA Registry, the incidence of either intimal tear (not a complication) or coronary dissection (a complication) was significantly higher in women, with PTCA of the right coronary artery, in patients with multivessel disease, and in those with tubular, nondiscrete, or eccentric lesions (Ref. 2 in Rogers' letter). It is likely that the higher incidence in women was related to smaller vessel size. Although data on vessel size are not available in the registry, body size has been shown to correlate with coronary artery size[1] and women in the registry were significantly smaller than men (mean body surface area: 1.70 vs 1.96, $p < 0.001$). Despite these size differences, a 3.0-mm balloon was the smallest one available during most of the registry experience and was used in most men and women. A relation between vessel size and the higher incidence of tear/dissection with right coronary artery PTCA, multivessel disease and specific lesion morphology is not evident from the registry data.

The question of appropriate matching of balloon size and vessel size addresses an important issue in view of the variety of balloon sizes currently available and the expanded application of coronary angioplasty to smaller vessels and more distal lesions. Individualization of balloon size selection is a sound approach that should be strongly recommended. It is likely that the risk of major plaque disruption and occlusive dissection is higher with overdilatation, and proper balloon/vessel sizing should reduce the occurrence of overinflation. However, precise determination of vessel size is confounded by the substantial degree of physiologic vasoreactivity of the coronary vasculature. These vessels are frequently significantly larger in caliber at the time of angioplasty compared with their size at diagnostic angiography, which is likely due to the liberal vasodilator therapy administered in conjunction with PTCA. Estimation of vessel size, therefore, will often represent only a rough approxi-

mation of vessel caliber and may underestimate lumen diameter at the time of dilatation. In addition, balloon size frequently increases beyond the specified predetermined diameter at high inflation pressures due to the compliance characteristics of the balloon material, so that overdistention may occur at high pressures despite appropriate balloon size selection. With these qualifications in mind, it is nevertheless desirable to individualize balloon size selection to approximate an optimal inflation diameter for each vessel segment to be dilated. The method of sizing using angiographic catheter French size suggested by Rogers provides a simple and practical approach for balloon catheter selection.

The potential role of relative balloon size to optimal arterial lumen diameter as a determinant of either dissection or restenosis should be carefully evaluated. Although overdilatation may be associated with an increased risk of dissection, the incidence of restenosis appears to be lower when a more complete dilatation is achieved. This is suggested from the registry report on restenosis, which demonstrated a significant relation between the residual gradient after PTCA and the frequency of restenosis (Ref. 5 in Reply above). Evaluation of the effects of procedural factors such as relative balloon size, maximal inflation pressure, and duration of inflation on acute outcome and restenosis using currently available catheter systems is clearly needed and should be of considerable value toward further improving early and long-term results with coronary angioplasty.

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Richmond, Virginia
13 October 1984

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SYMPATHETIC TONE IN CONGESTIVE HEART FAILURE

The study by Swedberg et al,[1] which attempted to assess myocardial catecholamine balance in patients with congestive heart failure (CHF), had major methodologic flaws. As Swedberg et al stated, the disposition of norepinephrine (NE) (after release) is complex, the spillover to plasma being determined by both neural release and neuronal and extraneuronal uptake. Their calculations did not take account of these factors. Because NE is both released to and extracted from plasma, a simple proportional decrement in concentration is not an acurate measure of extraction. The use by Swedberg et al of the Fick equation (uncorrected for NE extraction) to derive "NE release" was inappropriate for the same reason. Finally, the combination in their calculations of plasma catecholamine concentrations and whole blood rather than plasma flow was inappropriate.

Swedberg et al rejected the possibility that their results were influenced by the diuretic therapy of patients with CHF, because one-third of their control subjects were taking a diuretic drug. Most of the study group appeared to have taken a loop diuretic for CHF, whereas at least some of the control group took a thiazide diuretic for systemic hypertension. Diuretic therapy does increase NE turnover.[2] The possibility that therapy influences the results of Swedberg et al cannot be excluded.

An alternative method, which does account for both NE release and extraction, exists for the estimation of total and regional sympathetic tone.[3,4] A tracer infusion of ^{3}H-NE allows the calculation of release (R_{NE}) and clearance (C_{NE}) of NE:

$$R_{NE} = \frac{\text{rate of infusion (dpm/min)}}{\text{specific radioactivity of plasma (dpm/pg)}}$$

and

$$C_{NE} = \frac{\text{rate of infusion (dpm/min)}}{\text{plasma } ^3\text{H-NE concentration (dpm/ml)}}$$

Plasma flow is calculated from blood flow and the arterial hematocrit. Regional extraction of ^{3}H-NE (E_{TRIT}) is used to correct the Fick equation in the calculation of regional NE release: $Reg_{NE} = [(NE_V - NE_A) + NE_A \cdot E_{TRIT}] \times$ organ plasma flow. The methods have been used to evaluate sympathetic function in normal humans,[5] and in patients with essential hypertension,[4] thyroid disease,[5] autonomic insufficiency[2] and hepatic cirrhosis.[6] The effects of sympathetic and antidepressant drugs have been studied.[2,6]

It is appropriate and desirable that studies of regional sympathetic tone be performed in patients with CHF. However, it is essential that such invasive studies separate the effects of the disease from those of its treatment, and use a method that takes account of the bidirectional fluxes of NE in tissues.

Gregory J. Hasking
Murray D. Esler
Garry L. Jennings
Melbourne, Australia
3 January 1985

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REPLY: We greatly appreciate the criticisms and suggestions of Hasking, Esler and Jennings regarding our report on myocardial catecholamine balance in CHF. We are aware of alternative methods to assess total and regional sympathetic tone with the use of tracer infusion and completely agree that without the knowledge of neural release and neuronal and extraneuronal uptake, the significance of increased myocardial norepinephrine release in patients with CHF remains uncertain. We like to reemphasize that our study did not report the "disposition of norepinephrine after release" and this has been stated as Hasking et al noted. The catecholamines were assayed by radioenzymatic method, the validity of which is well known. The hematocrits in the 2 groups of patients were virtually identical. Thus, estimation of net myocardial NE release, by determining the coronary sinus blood flow, appears to be a valid technique.

Although it is known that diuretic therapy can influence catecholamine release, we did not find in our patients any differences in the catecholamine concentrations in relation to the diuretic therapy. Thus marked increase in NE concentration in coronary sinus venous blood and an approximately 20-fold increase in net myocardial NE release in patients with overt CHF cannot be explained by diuretic or any other prior pharmacologic intervention. We agree that without further studies, as suggested by Hasking et al, the significance of the enhanced myocardial NE release remains uncertain.

Kanu Chatterjee, MB, FRCP
San Francisco, California
29 January 1985

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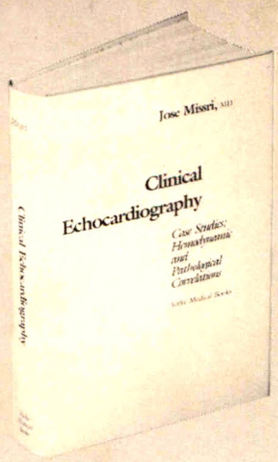

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REFERENCE: 1. Needleman P, Johnson EM Jr: Vasodilators and the treatment of angina, in Gilman AG, Goodman LS, Gilman A (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc, 1980, pp 819-833.

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MIAMI: Metoprolol in Acute Myocardial Infarction

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MIAMI: Metoprolol in Acute Myocardial Infarction

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Foreword

During the last 20 years a very large number of studies have been published on the effects of β-adrenoceptor blocking agents in patients during and after myocardial infarction. According to a recent review,[1] there are at least 65 such trials including about 50,000 patients. In addition there are some studies in progress or not yet fully reported.

Prophylactic institution of β blockers after myocardial infarction is of proven value and the pooled results of all placebo-controlled trials show a very significant reduction of 25% in mortality at 1 to 2 years. A similar reduction was also obtained for reinfarctions. Most of the studies are of the late-entry type, with start of treatment 1 to 2 weeks after onset of infarction. The most convincing studies were the 3 large trials on timolol,[2] metoprolol[3] and propranolol[4] published in 1981; each showed a significant reduction in total mortality.

During the acute phase of myocardial infarction, mainly during the hospital stay, many studies have demonstrated favorable effects of β blockers on chest pain, infarct development, arrhythmias, hemodynamics and tolerance, but few have investigated mortality and morbidity. Only 1 study, The Göteborg Metoprolol Trial,[3] has shown positive effects on early mortality, and the effects were significant at 3 months. This trial also showed beneficial effects on all clinical variables studied.[5] Based on the results of this trial the MIAMI (Metoprolol in Acute Myocardial Infarction) Trial was designed to study further the effects of metoprolol therapy on mortality and morbidity during the first 15 days after onset of symptoms in patients with suspected myocardial infarction. The major results of this trial were recently published;[6] the present symposium proceedings are a comprehensive and final report on all findings during the 15-day trial period.

The MIAMI Trial was made possible by excellent collaborative work among committee members, investigators, doctors, nurses and other personnel in 104 hospitals in 17 countries. On behalf of the members of the Steering Committee, I express our sincere thanks for their cooperation.

Åke Hjalmarson
Chairman of the Steering Committee
The MIAMI Trial Research Group

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Metoprolol in Acute Myocardial Infarction (MIAMI)

Introduction

The MIAMI Trial Research Group

In the Western world, coronary artery disease constitutes the single most common cause of death in middle-aged men and women. This remains so despite a recent decline in mortality from the disease in some countries, including the United States.[1] The mortality rate from acute myocardial infarction (AMI) during the hospital stay usually ranges between 10 and 20% in unselected groups of patients younger than 70 years of age.[2] The magnitude of the problem has led to the planning and realization of a number of trials aimed at assessing the effectiveness of various interventions to reduce mortality and new events. The first clinically useful β blocker, propranolol, became available in 1964. Shortly thereafter, Snow[3] published the results of an open study with propranolol in 93 patients after AMI, showing a significant reduction in mortality. Subsequently many trials have evaluated the effect of β blockade on survival, during both the acute stage of myocardial infarction and the long-term follow-up.[4–13]

The methodology of clinical trials has undergone considerable refinement during the last decade. An increasing number of well-controlled and organized trials have presented evidence that β blockade may reduce long-term mortality, sudden death or reinfarction in patients with myocardial infarction.

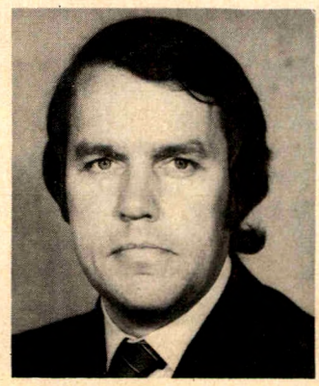
Since Snow's publication, several randomized, prospective, double-blind studies, each with more than 100 patients, have been performed and have not confirmed his findings regarding the early mortality reduction within a few weeks after onset of myocardial infarction.[14–20]

Only 2 placebo-controlled, early-entry studies with mortality reduction as a major objective have been published.[8,10] In these studies most patients were included within 12 hours after onset of symptoms indicating AMI. Neither study was able to show a significant reduction in the short-term mortality, i.e., within 2 to 3 weeks after onset of AMI, nor were they designed for this particular purpose. In the Copenhagen Alprenolol Study[8] the mortality was reduced only in patients younger than 65 years after 1 year of treatment. In the Göteborg Metoprolol Trial[10] a significant reduction in mortality was seen for all age groups after 3 months.

Early intravenous administration of metoprolol (within 12 hours) has been shown to favorably influence various indexes associated with infarct size.[21–23] Further, it has been shown to reduce ischemic chest pain,[24] need of analgesics[24] and signs of impaired left ventricular function.[25] The finding of a shorter hospital stay might be explained by these effects.[21] Another important action of metoprolol appears to be a marked reduction of serious ventricular arrhythmias.[26] Some of these findings have been reported with other β blockers.[27–30].

At the time of planning the present study the question of whether it was possible to markedly reduce the short-term mortality, e.g., during the first 2 weeks (essentially the hospital period) remained unanswered.

In a subgroup of patients from the Göteborg Metoprolol Trial, all of whom had an entry heart rate $\geq$70 beats/min, systolic blood pressure $\geq$110 mm Hg and no earlier β-blockade therapy, there was a 45% reduction in mortality as early as 15 days after inclusion, from 7.0% in the placebo group to 3.8% in the metoprolol group. The number of such patients, however, was



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too small for that study to provide conclusive results, and the findings were from retrospectively designed analyses.

Based on the experience from the previous Göteborg Metoprolol Trial,[10] a new study involving a larger group of patients was necessary to answer conclusively the question of whether it was possible to reduce the short-term mortality during the hospital period in AMI patients. This trial was named "Metoprolol in Acute Myocardial Infarction" (MIAMI). The patients were allowed to enter if they were not undergoing treatment with β blockers, had a heart rate >65 beats/min and a systolic blood pressure >105 mm Hg. In order to particularly demonstrate the effects of metoprolol during the early phase, variables other than death were investigated.

It should be stressed that these patients could not be expected to be representative of the entire myocardial infarction population generally seen in coronary care units. It might also be expected that correlations between some variables (e.g., heart rate and blood pressure) and outcomes reported in other studies might be distorted or not demonstrable because of this selection.

With this background and previous experience, particularly the Göteborg Metoprolol Trial,[10] the following primary and secondary objectives were selected.

The primary objective was to evaluate whether metoprolol could reduce the mortality from all causes over the period of 15 days (the trial period) in patients hospitalized with a suspected or definite AMI.

The secondary objectives were to assess the effect of metoprolol on the sum of both deaths and patients with nonfatal ventricular fibrillation (VF) during the first 5 days; enzyme-related infarct size within 3 days (days 0 to 3); incidence of definite AMI within 3 days (days 0 to 3); incidence of late first infarctions during the trial period (days 4 to 15); incidence of recurrent infarctions during the trial period (days 4 to 15); incidence of definite AMI during the trial period (5 and 15 days) in patients with and without electrocardiographic signs of infarction on admission; incidence of VF (nonfatal and fatal, number of patients and episodes) and presence of left ventricular heart failure/congestive heart failure (number of patients and use of diuretics) and chest pain (pain duration and use of analgesics) during 5 days and 15 days; and tolerance, safety and adverse events during 5 days and 15 days.

Further, a number of retrospective analyses were made to determine whether the effect of metoprolol was related to entry heart rate, site of suspected infarction and interval between onset of symptoms and start of treatment (subgroup hypotheses).

Some of the main findings of the MIAMI trial have been published previously.[31] This *American Journal of Cardiology* supplement is intended to provide a detailed reporting of the results relating to the basic protocol.

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Patients and Methods

The MIAMI Trial Research Group

The effects of early intervention with metoprolol in patients with suspected or definite acute myocardial infarction (AMI) have been assessed in a randomized, double-blind, placebo-controlled international study. Patients aged 75 years or younger were eligible for entry if they presented to a coronary care unit within 24 hours of the onset of symptoms of an AMI. Exclusion criteria included current treatment with a β blocker or calcium-channel blocker, heart rate ≤65 beats/min, systolic blood pressure ≤105 mm Hg, contraindications and other administrative reasons. Treatment began with an intravenous loading dose (3 × 5 mg injections of metoprolol or placebo at 2-minute intervals) followed by an oral regime of 200-mg metoprolol daily or placebo. The study period was 15 days in addition to the day of randomization. The patients' clinical history and status at entry were documented. The following outcome variables were recorded: mortality, development of AMI, serum enzyme activity, electrocardiographic signs of AMI, late or recurrent AMI, arrhythmias, treatment of chest pain, concomitant treatment, adverse events and details of treatment with trial medication.

(Am J Cardiol 1985;56:3G–9G)

The trial was double-blind and placebo-controlled. The day of randomization was day 0 and the trial period was defined as days 0 through to and including day 15. Each study day was a 24-hour calendar day, except day 0, which was always less than 24 hours. The important elements of the design of the trial were contained in the final project protocol (dated November 16, 1982), which is available from the authors upon request.

Patients

Selection: All men and women 75 years old or less with either chest pain of acute onset and a suspicion of acute myocardial infarction (AMI) of at least 15 minutes duration, or electrocardiographic signs and symptoms indicating an AMI had occurred within the last 24 hours were eligible for inclusion in the study.

Screening: All patients admitted to coronary care units who were eligible for inclusion were registered in consecutive order in a specific "MIAMI Log Book." The patients were then evaluated with regard to specific exclusion criteria (Table I). The exclusion criteria were evaluated in a hierarchic order according to Table I and the criterion carrying the lowest number was listed for each excluded patient. The reasons for exclusion could be divided into 3 major groups; first, treatment with either β blockers or calcium-channel blockers, second, conventional β-blocker contraindications and third, exclusions for technical and methodological reasons. The MIAMI Log Book was a source of information on all eligible patients. In it, the following information was recorded for all patients: date of arrival, name, year of birth, exclusion criterion or randomization number, date of randomization and whether or not a myocardial infarction was confirmed during the hospital stay. The log book permitted comparison of patients selected for randomization with the excluded patients.

Randomization: All eligible and not excluded patients who had given their informed consent were then randomly allocated to treatment with placebo or metoprolol.

Conduct of the Trial

The clinical management of all symptoms and complications was to be conducted according to local practice. However, certain general recommendations were given in a manual of procedures, which is available from the authors upon request.

Randomization procedure: As soon as possible after the patient had been admitted to the coronary care unit, baseline electrocardiogram (ECG), heart rate and systolic blood pressure were monitored over at least a 10-minute interval. Physical examination including pulmonary auscultation was also performed.

If no exclusion criteria as listed in Table I were met, the patient was then considered suitable for random-

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TABLE I Exclusion Criteria

Current treatment with β blockers (any treatment within the previous 48 hours)
Current treatment with calcium-channel blockers (any treatment within the previous 48 hours)
Heart rate ≤65 beats/min during the 10-minute interval
Systolic blood pressure ≤105 mm Hg during the 10-minute interval
Left ventricular heart failure with basal pulmonary rales >10 cm
Signs of poor peripheral circulation, such as coldness and paleness, due to pump failure
AV conduction with P-Q time >0,24 second or higher degree AV block
Severe chronic obstructive pulmonary disease (e.g., requiring long-term treatment with corticosteroids or β_2 stimulants)
Implanted pacemaker
Resuscitation outside hospital (within 24 hours)
Other serious diseases influencing short-term prognosis and general condition (e.g., neoplasm, severe organ insufficiency, cerebral lesions)
Previous participation in MIAMI trial
Participation in other randomized trials
Unwillingness to participate in trial or unable to give informed consent

AV = atrioventricular.

TABLE II Reasons for Temporary and Permanent Withdrawal

Temporary withdrawal
SBP ≤89 mm Hg (caution should be taken with regard to patients with previous hypertension)
Heart rate ≤44 beats/min *and* concomitant signs suggestive of depressed heart function (e.g., SBP ≤89 mm Hg, signs of poor peripheral circulation and pulmonary congestion)
P-Q time >0.26 second
Asystole not related to administration of narcotic analgesics or following defibrillation
Persistent basal lung rales >10 cm despite optimal treatment
Permanent withdrawal
Use of sympathomimetic drugs for the above listed conditions
Asystole, bradycardia or AV block requiring permanent pacemaker insertion
Frequent or severe anginal attacks (e.g., 5 to 10/day) in spite of vigorous treatment with antianginal drugs except β blockers
Supraventricular tachyarrhythmias requiring open treatment with β blockade
Significant bronchial obstruction despite additional treatment with β_2 stimulants

AV = atrioventricular; SBP = systolic blood pressure.

ization. The trial medication was immediately made ready and the cardiovascular status of the patient checked again. If there was still no reason for exclusion, the ampoule containing the intravenous trial medication was opened, and at this point the patient was defined as being randomized into the study.

Trial medication: The intravenous administration of trial medication was given as soon as possible after randomization as 3 rapid injections of 5 ml each (5 mg metoprolol or matching placebo), with 2-minute intervals. Heart rate, systolic blood pressure and ECG were monitored during intravenous administration and 15 minutes thereafter. Before the second and third injections were given, the heart rate should have been >49 beats/min, the systolic blood pressure >99 mm Hg and the P-Q time <0.26 second. Further, it was required that there was no worsening of dyspnea or cold sweating before the second or third intravenous dose was given. If the patients fulfilled these criteria and had no aggravation of dyspnea or cold sweating 15 minutes after completion of the full intravenous injection (15 ml), one-half of the trial tablet (metoprolol 100-mg tablet or matching placebo) was then given.

The standard dose was one-half tablet every 6 hours over days 0 to 2 and thereafter 1 tablet every 12 hours for the remainder of the trial period. Instructions regarding administration and adjustment of trial medication were given in the manual of procedures.

Patients who received a reduced dose of oral medication or no dose during the first 2 days were reassessed for institution of treatment on day 3. Inclusion day is registered as day 0. After day 2, 100-mg metoprolol or placebo was given twice a day until at least day 16. Thereafter, it was recommended that all patients were to be treated openly with metoprolol.

Withdrawal of trial medication: Predetermined guidelines for withdrawal of trial medication and instructions for treatment of different complications and symptoms were specified in the manual of procedures. The criteria for temporary and permanent withdrawal are listed in Table II. If treatment was temporarily withdrawn, the patient was reassessed 2 days later for gradual reinstitution of trial medication. The patient was permanently withdrawn if the medication was withdrawn a second time.

The main principle was to maintain the patients on trial medication, or in case of withdrawal, to reinstitute the medication if possible. The goal was to have the patients on the highest tolerable dose of trial medication throughout the trial period.

Concomitant therapy: The drugs generally used in the treatment of patients with AMI were allowed as described in the manual of procedures. However, the use of other drugs that may have interfered with the evaluation of treatment effects was avoided, especially where a potentially hazardous drug interaction existed. On the other hand, there was an attempt not to be too restrictive in the use of concomitant therapy because an unnecessary high withdrawal of trial medication might have resulted. All β-blocking agents, verapamil and diltiazem were not to be given to patients on trial medication with the exception of verapamil in patients with supraventricular tachyarrhythmias and without left ventricular failure.

Study Variables

All randomized patients were documented according to a standardized Basic Case Report Form (BCRF). Patient information on general clinical history, long-term cardiovascular drug treatment, signs of myocardial infarction on the ECG, treatment in hospital before randomization and clinical status immediately before the blind injection (pulmonary rales, atrial fibrillation, heart rate and systolic blood pressure) was recorded on the BCRF. All effect variables were documented in the BCRF.

Heart rate and systolic blood pressure immediately before blind injection and 15 minutes after completed intravenous administration were documented. A standard ECG was obtained immediately after arrival in hospital. The ECG was continuously monitored over a 10-minute period before and during the injection procedure, and thereafter according to the local routine. The ECG signs were recorded on the BCRF.

The following definitions were used:

Q wave = ≥0.04 second wide and >1 mm deep, or ≥0.03 second wide and Q/R >1/3 and >1 mm deep.

ST-segment elevation = ≥1 mm in leads I, II, III, aVL, aVF, V_5 and V_6, or ≥2 mm in leads V_1, V_2, V_3 and V_4.

Loss of R wave = complete loss of R wave with a reduction in R-wave amplitude of at least 3 mm in 2 electrodes or more, which remained in at least 2 consecutive recordings.

Serum enzyme tests according to the local practice were required once a day during days 0 to 3, and the maximal value was recorded.

Definite acute myocardial infarction (days 0 to 3): Definite AMI was diagnosed if 2 or 3 of the following criteria were fulfilled: (1) chest pain with a duration of at least 15 minutes; (2) two values above the normal range for the enzyme used for infarct definition; and (3) appearance of new Q waves or loss of R waves or ST-segment elevation followed by T-wave inversion in at least 2 electrodes in a 12-lead standard ECG.

Possible acute myocardial infarction (days 0 to 3): Possible AMI was diagnosed if chest pain of at least 15 minutes' duration occurred and any one of the following criteria was fulfilled: (1) appearance of T-wave inversion in at least 2 electrodes in a 12-lead standard ECG without enzyme values above the normal range; (2) only 1 raised enzyme value above the normal range; and (3) appearance of new Q waves or loss of R waves or ST-segment elevation followed by T-wave inversion in only 1 electrode in a 12-lead standard ECG.

Localization of definite myocardial infarction: Definite myocardial infarction was classified as anterior, lateral, inferior, posterior wall infarction or other (to be specified) according to the following definitions:

Anterior wall infarction = criteria for definite myocardial infarction fulfilled in any of the leads V_1 through V_4 in a 12-lead standard ECG.

Lateral wall infarction = criteria for definite myocardial infarction fulfilled in any of the leads V_5 through V_7, I or aVL in a 12-lead standard ECG.

Inferior wall infarction = criteria for definite myocardial infarction fulfilled in any of leads II, III or aVF.

Posterior wall infarction = increase in R-wave in leads V_1 or V_2.

For purpose of presentation, the recorded localizations have been grouped in the following fashion. All anterior includes anterior together with other locations except inferior. All inferior includes inferior together with other locations except anterior. Other locations include other locations, lateral, posterior and anterior together with inferior. Pure anterior and pure inferior have also been presented.

The occurrence of late first or recurrent infarctions during the study periods days 4 to 5 and 6 to 15 was also recorded with application of the same definition for definite myocardial infarction as previously given.

Ventricular fibrillation (VF): The time of each episode of VF was recorded during days 0 to 15. When multiple episodes of VF occurred, a free interval of 2 minutes or more was required before a new episode was registered for analysis. End-stage VF occurring within 24 hours of death was defined as agonal and not included in the analysis if refractory left ventricular failure or cardiogenic shock was present. Clinical observations were recorded based on 2 time intervals: 0 to 5 days and 6 to 15 days.

Occurrence of auscultatory basal pulmonary rales (more than sparse rales) indicating congestive heart failure and requiring treatment was noted. The use of any diuretics was documented. Additionally, the total dose of furosemide if used or the calculated equipotent doses of other diuretics as well as the number of injections were recorded. The time of last narcotic analgesic injection was recorded as well as the number of injections.

Hypotension, bradycardia, atrioventricular block, pacemaker insertion, supraventricular tachyarrhythmia, ventricular tachycardia, asystole, cardiogenic shock and different cardiac medications were noted.

Temporary and permanent withdrawal of trial medication was noted as were the reason and the time of permanent withdrawal. Adverse events possibly related to the trial medication were recorded. The exceptions were hypotension, bradycardia, heart failure and atrioventricular block.

The patient's compliance with treatment was judged by tablet counts. The days on which patients received full dose, half dose, quarter dose and no dose were also registered.

Information on time, place, cause and mode of death was recorded. The occurrence of cardiac rupture was documented in all patients in whom autopsy reports were available.

The primary endpoint in the trial was death from all causes during the trial period, days 0 to 15.

The secondary endpoints were: (1) the sum of both deaths and patients with nonfatal VF during days 0 to 5; (2) definite myocardial infarction during days 0 to 3; (3) infarct size estimated from serum enzymes during the first 3 days; (4) definite myocardial infarction from days 0 to 5 and days 0 to 15; (5) late first infarction during days 4 to 15; (6) recurrent infarction during days 4 to 15; (7) cardiac death and mode of death during days 0 to 5 and days 0 to 15; (8) noncardiac death during days 0 to 5 and days 0 to 15; (9) incidence of VF (both nonfatal and fatal, number of patients and episodes) and presence of left ventricular heart failure/congestive heart failure (number of patients and use of diuretics) and chest pain (pain duration and use of analgesics) during days 0 to 5 and days 0 to 15; and (10) tolerance, safety and adverse events during days 0 to 15.

TABLE III The Responsibilities of the Steering Committee

Preparation of the study protocol, case report forms and manual of procedures
Recruitment of investigators and provision of guidance to the trial centers
Making all ethical, scientific and policy decisions
The practical running of the study
Acting upon recommendations of the Safety Monitoring Committee
Collecting, editing and storing all data received from the trial centers
Monitoring and maintaining quantity and quality of data flow
Preparing the periodic progress reports for the Advisory Committee and trial centers
Preparing reports from the trial for publication
Blind classification of all endpoints

Organization

A formal organizational plan was established (Fig. 1). Steering, Advisory, Safety Monitoring and Independent Data Audit Committees were formed. The Steering Committee also established 4 different subcommittees: Economy and Administration, Statistical, Data Coordinating and Data Management.

The Steering Committee consisted mainly of investigators from the Göteborg Metoprolol Trial.[1] The Steering Committee was primarily responsible for preparation of the project protocol, BCRFs and manual of procedures. This committee was also responsible for recruitment of investigators. The responsibilities of the Steering Committee are listed in Table III. A Publications Subcommittee was formed from within the Steering Committee.

The Advisory Committee was selected by the Steering Committee and consisted of experienced cardiologists from different participating countries. The Advisory Committee was responsible for approving the scientific and ethical design of the study and advised the Steering Committee on major policy decisions. The Advisory Committee also reviewed the scientific reports before publication.

The Safety Monitoring Committee was selected by the Steering Committee and was composed of 3 physicians with training in epidemiology and clinical trial methodology and 1 statistician.

An important function specified in the protocol was that the Safety Monitoring Committee would carefully monitor the results at regular intervals to detect as soon as possible any harm from the treatment, which would cause premature closure of the trial. The protocol also stated that because such periodic monitoring was associated with an increased risk of a false-positive finding, the method of O'Brien and Fleming[2] in deciding a statistically significant result was to be used. The Safety Monitoring Committee analyzed selected endpoints after approximately 1,500, 2,000, 3,000 and 4,000 patients were randomized, and found no cause to recommend a premature termination of the study. The results of these analyses were kept within the Safety Monitoring Committee except for the data of the 4,000 patients, which were discussed confidentially with the Advisory Committee.

Other responsibilities included reviewing and endorsing general methodology and statistical analyses, and presenting periodic reports to the Steering Committee.

The Independent Data Audit Committee, selected by the Steering Committee, consisted of a statistician located in Oslo, Norway. He was responsible for checking and notification of randomized patients and deaths. These data were obtained directly from each trial center. This committee guaranteed that no technical errors or erroneous statistical analyses were made in relation to objectives stated in the project protocol. Site visits were made to the Data Management Center during the trial to ensure correspondence between these 2 data bases and to audit procedures.

One hundred and four centers from 17 countries participated in the MIAMI trial. The Data Coordinating and Data Management Subcommittees were merged early after starting the study to form a Data Management Center in Göteborg, which was composed of scientific and administrative staff of AB Hässle and a data auditor appointed by the Steering Committee. Local data centers were established in each

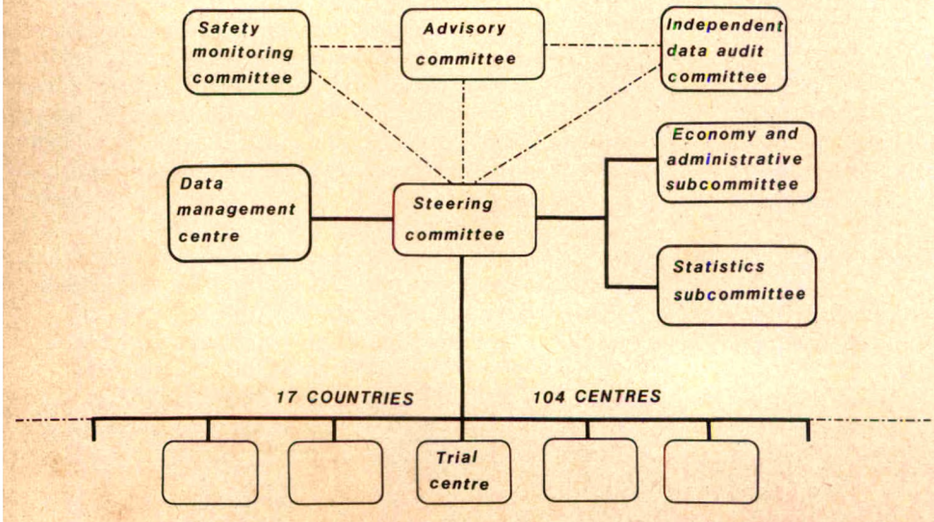

FIGURE 1. Plan of MIAMI trial organization.

participating country and were staffed by clinical trial monitors from the local Astra companies. This project organization was responsible for constructing and continuously updating a computerized data base of all study variables.

The protocol was reviewed and approved by the responsible ethical review committee at each of the participating trial centers. At all trial centers the patients were fully informed regarding the trial and consented to participate, at least verbally.

Statistical Methods and Analyses

In estimating sample size, a 7% mortality rate was assumed for the placebo group. To detect a 35% reduction in mortality in the metoprolol group with 90% probability using a 2-sided test at the 5% significance level, it was calculated that 4,000 patients with a suspected myocardial infarction at entry were needed. This would yield approximately 2,400 patients (60%) with a confirmed diagnosis of AMI. Because patients could be entered before their presumed myocardial infarction status was confirmed, a substantial portion of patients without a definite myocardial infarction were expected to be randomized.

Because this trial was to be conducted in several countries, there was uncertainty regarding the applicability of the just mentioned assumptions about mortality and the percentage of definite myocardial infarctions derived from previous smaller studies mostly performed in Scandinavia. The consequent impact may have been a smaller number of events than anticipated, and so to compensate for this loss of statistical power, an increase of sample size was allowed for. If the average mortality rate for the 2 treatment groups was <5% when 2,000 patients had been randomized, the sample size was permitted to be increased to 5,200 patients. This would have corresponded approximately to 3,200 patients with definite myocardial infarctions. This increase would have given a 90% probability of establishing a 35% difference as significant if the mortality was only 5% in the placebo group.

The statistical test of the 15 day mortality was done with Fisher's exact test in 4-fold tables. Mantel-Haenszel's method was used to test differences in survival curves. A 2-tailed test with a p value ≤ 0.05 was regarded as significant. The nominal p values rounded to 2 most significant digits have been presented when <0.10 throughout.

Subgroups were formed based on certain baseline and diagnostic variables. Quantitative variables were dichotomized at the quartiles or the median. Differences were tested with Fisher's exact test, 2-tailed. The p-value conventions just described were applied.

Some subgroups were proposed in the protocol (subgroup hypotheses) and others formed retrospectively. These differentiations are stated in reporting the results.

Multivariate analyses: For such binary response variables as death, definite myocardial infarction and use of narcotic analgesics, the effect of drug and important baseline variables and possible interactions between drug and baseline variables have been analyzed with logit models.[3] Logit analysis of categorical data can be looked upon as a counterpart of regression analysis of continuous response variables.

The analysis began with a basic set of predictors, proceeded with the fit of an adequate model based on previous knowledge and expectations and included main effects of the predictors and reasonable interactions between drug and other predictors. Tests similar to those performed in regression analysis were done to test the significance of individual predictors.

This multivariate model approach, which simultaneously considers the effect of all variables in the basic set, is much more appropriate than a subgroup analysis in which only 1 predictor at a time is taken into consideration. The multivariate analysis avoids the confounding of effects of different variables as far as all relevant variables are included in the basic set. The multiplicity test problem is present but not to the same extent as with a detailed subgroup analysis.

The requirement for an adequate model fit was set to $p > 0.15$ and the significance level for the test of the effect of individual predictors was set to 5%.

Randomization code: All patients included in the trial were given a consecutive patient randomization number that was printed on the trial medication ampoules and bottle. The randomization code was stratified only by trial center. The randomization code was computer-generated on a microcomputer by a member of the Safety Monitoring Committee, independently of all other organizing committees and the sponsor of the trial. Only 4 sets of the randomization code were generated, 1 for the Chairman and 1 for the statistician of the Safety Monitoring Committee, 1 for the Pharmacy Department at the Östra University Hospital whose members were responsible for packing the clinical trial material and 1 for emergency use. This last code was provided sealed in separate envelopes for individual patients at each trial center. The code list was produced in blocks of 50 and towards the end of the study in blocks of 16.

Each block contained equal numbers of patients on the 2 treatments randomly ordered in such a way that the difference in numbers on placebo and metoprolol never exceeded 3 when starting from the beginning of the block. This enabled a good balance to be achieved within each center. The block constituted different random permutations of the treatments with the 2 restrictions mentioned above.

Packaging and Distribution of Trial Medication

For each randomized patient there were 4 ampoules of 5 ml (metoprolol tartrate 1 mg/ml or normal saline placebo) and a bottle containing 40 tablets (metoprolol tartrate 100 mg or placebo). These formulations were supplied by AB Hässle, a subsidiary of AB Astra, Sweden.

Packaging and labelling according to the randomization code were done in the Department of Pharmacy of the Östra University Hospital in Göteborg. The stock was packaged in sets of 50, together with the individual code sealed in 50 separate envelopes and with the BCRFs, and then distributed to the trial

centers. The procedure was performed in this way so that the study could be conducted blindly by the organizing committees, the investigators, the patients and the sponsor.

Data Management and Monitoring Procedures

The data collected by each trial center were recorded on 4 different case report forms. A patient recruitment information slip containing randomization number and date was completed when a patient was randomized and copies were distributed according to Figure 2. Within a few weeks, the Data Management Center and the Independent Data Audit Committee were informed of each patient who had entered.

Copies of the log book and BCRF were distributed according to Figure 3. The BCRF was a 9-page booklet; the first 8 pages were in 3 copies (white, blue and yellow) and the ninth page had 4 copies (white, blue, yellow and pink). Completed log books and BCRFs were collected personally by a study monitor approximately every month and thus within 2 months of randomization, these data were usually at the Data Management Center. The Independent Data Audit Committee received the mortality data on the pink copy of page 9 of the BCRF within a similar time.

Quality control and data base procedures: BCRFs completed at the trial center and signed by designated investigators were subject to quality checks at these stages:

Stage 1 at the trial center, by the Astra monitor. Uncertainties were clarified before copies were removed.

Stage 2 at the Data Management Center in Sweden, by a data auditor appointed by the Steering Committee. Uncertainties were noted on a data clarification form, which was returned to the trial center for clarification.

Stage 3 at the Data Management Center, using a computerized input and editing system (CHIVAS [Computerized Hässle Input, Validation and Access System]). This system used a screen form of each page of the BCRFs as an entry mode and provided error reports on missing data, out-of-range data and internal inconsistencies within a patient's data. Errors detected were noted on a data clarification form and returned to the trial center for clarification.

Stage 4 at the Data Management Center, using editing programs on the data base. After data had been entered to the data base via CHIVAS, extensive checks were conducted using programs to identify any logical inconsistencies that the CHIVAS system could not detect during the input phase. Uncertainties were clarified by the trial center using a data clarification form as described previously.

Data base integrity: During the validation and input phase, conventional data processing routines for confidential data were applied, i.e., only authorized staff had access to the data. Access to the computer programs was further restricted by means of a series of passwords changed frequently.

A data control document was used to record the transfer of responsibilities, the dates for completion of the scheduled actions and the detected error rates. The data control document was stored together with the case report form to serve as an independent check that the data base remained intact.

Data file transfer: After patient recruitment ended on March 31, 1984, and the 15 days' follow-up was completed, all log book and BCRF data were entered and validated in the data base using the just described procedures by early May 1984. At this time the Independent Data Audit Committee corroborated the number of randomized patients and mortality data in the data base at the Data Management Center and approved the start of the data analysis. The data file was then transferred from the Data Management Center to the University of Göteborg where, for the first time, the code was entered and analyses begun.

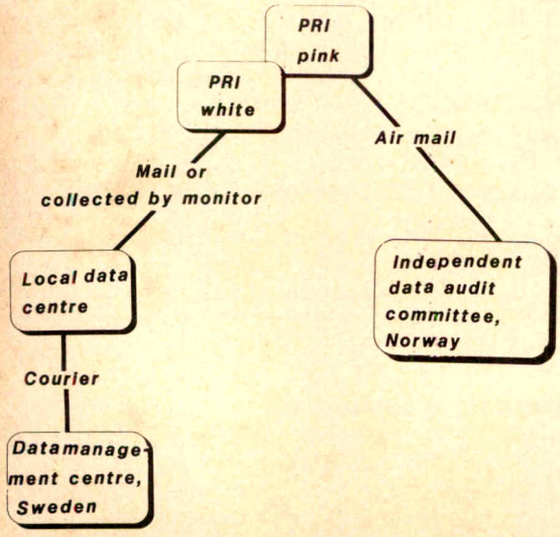

FIGURE 2. Flow chart for the patient recruitment information (PRI) forms.

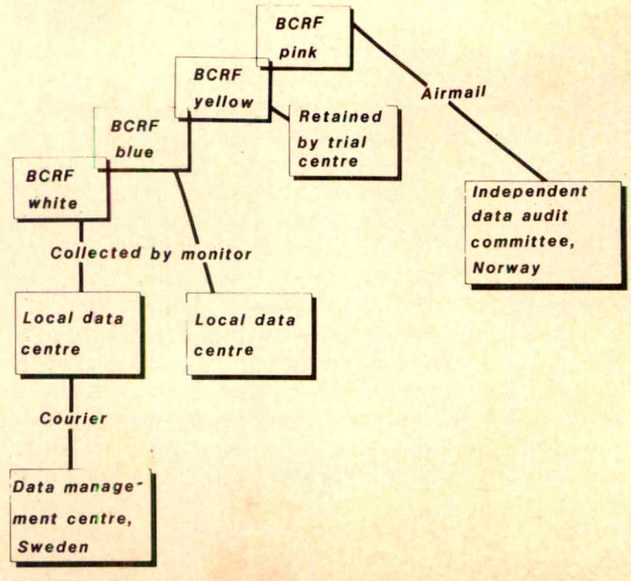

FIGURE 3. Flow chart for the basic case report forms (BCRFs).

In summary, a trial needs to include enough patients to yield a sufficient number of endpoints to allow statistical analysis at a satisfactory level of significance and with a reasonable likelihood of reaching that result. Only an analysis including all randomized patients regardless of subsequent fate is devoid of bias from the investigators and analysts.

It has been argued that the chronotropic effect of β blockers precludes the maintenance of blindness in placebo-controlled studies. It has also been proposed that the use of indisputable endpoints, such as death from any cause, would reduce bias such that a blinded design was unnecessary. In all studies of β blockers, the average heart rate in the β-blocker group of patients has to be lower than in the placebo group. However, the variance in both treatment groups has always been sufficiently great to cause a large overlap between the 2 groups. For this reason, there is uncertainty in the prediction of the actual treatment in any individual.

Maintenance of the highest possible degree of blindness was seen to be particularly important when it was shown that even nonspecific measures, such as good medical practice, may have a substantial impact on reinfarction and deaths without the use of any pharmacologic intervention.[4,5]

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Patient Population

The MIAMI Trial Research Group

During the recruitment phase of the MIAMI trial (December 1982 to March 1984), data on 26,439 patients eligible for inclusion were entered. Of these, 5,778 patients were included. Current treatment with either β blockers or calcium-channel blockers (51%) was the most predominant reason for exclusion. The randomized and excluded patients differed. The randomized patients were younger and more often men. The mean age of the patients was 59 years in both the placebo and the metoprolol groups. The 2 groups were evenly balanced with regard to basic demographic variables. The median delay between onset of symptoms and randomization was 7 hours, and 25% of the patients were included within 4 hours. Previous clinical history and pharmacologic treatment given before admission were well balanced in the groups. Mean heart rate for the 2 groups before randomization was 83 beats/min and systolic blood pressure was 141 mm Hg. Approximately 15% of randomized patients presented with pulmonary rales. Before randomization 20% of the patients had normal electrocardiograms; 70% could be classified as having electrocardiographic signs of acute myocardial infarction; and 10% presented with other electrocardiographic abnormalities. Electrocardiographic signs at entry suggested a predominance of anterior wall infarctions. The randomized patients were not representative of eligible patients and the treatment groups were well balanced at entry.

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This article will present the outcome of the patient selection procedure and compare the patient sample randomized into the MIAMI trial with the patients excluded. It also examines the comparability of the 2 treatment groups with respect to baseline characteristics. The methodology concerning patient screening and randomization was presented in full in the preceding article.

Results

During the recruitment phase of the trial, which took place between December 1982 and March 1984, data on 26,439 patients eligible for inclusion were entered into the MIAMI Log Books (Table I, Figs. 1 and 2). Of these, 20,661 were excluded. The remaining 5,778 patients did not meet any of the 14 exclusion criteria and were subsequently randomized into the study.

Current treatment with either β blockers or calcium-channel blockers was the most predominant reason for exclusion (51.1%). Other reasons for exclusion are listed in Table I.

Table II lists the reason for the exclusion of patients in various age categories. There was a positive correlation between increasing age and exclusion rate because of left ventricular failure, atrioventricular-conduction disturbances and chronic obstructive pulmonary diseases, while the reverse was true for those excluded

TABLE I Eligible Patients with MIAMI Log Book Inclusion and Exclusion Criteria (for patients with multiple exclusion criteria the first is listed)

Eligible patients		26,439 (100)
Excluded patients		
Current β-blocker treatment	8,205 (39.7)*	
Current calcium-channel blocker treatment	2,358 (11.4)	
Heart rate ≤65 beats/min	4,190 (20.3)	
Systolic blood pressure ≤105 mm Hg	1,081 (5.2)	
Left ventricular failure, rales >10 cm	1,422 (6.9)	
Poor peripheral circulation	164 (0.8)	
AV-conduction disturbance	439 (2.1)	
Chronic obstructive pulmonary disease	638 (3.1)	
Implanted pacemaker	115 (0.6)	
Out-of-hospital resuscitation	233 (1.1)	
Other serious disease	369 (1.8)	
Previous MIAMI trial participation	207 (1.0)	
Participation in other studies	167 (0.8)	
Unwillingness	1,063 (5.1)	
(Information missing)	(10)	
Total		20,661 (78.1)
Randomized patients		5,778 (21.9)

* Numbers in parentheses indicate percentages of all eligible or excluded patients.
AV = atrioventricular.

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TABLE II Percentage of MIAMI Log Book Exclusion Criteria in Different Age Groups

	Age (years)				
	<39	40–49	50–59	60–69	>70
Exclusion criteria					
Current β-blocker treatment	38.6	38.5	41.9	41.1	35.4
Current calcium-channel blocker treatment	9.1	8.6	10.8	11.9	12.7
Heart rate ≤65 beats/min	21.8	25.7	22.1	19.0	18.0
Systolic blood pressure ≤105 mm Hg	5.6	6.3	5.1	4.9	5.6
Left ventricular failure	1.6	3.4	4.7	7.2	10.8
Poor peripheral circulation	0.5	0.8	0.7	0.8	0.9
AV-conduction disturbance	1.4	1.8	1.7	1.9	3.1
Chronic obstructive pulmonary disease	1.9	1.8	2.3	3.7	3.5
Implanted pacemaker	0.2	0.2	0.4	0.6	1.0
Out-of-hospital resuscitation	1.4	0.9	1.2	1.1	1.1
Other serious diseases	2.3	0.8	1.5	1.8	2.5
Previous MIAMI inclusion	1.4	1.6	0.9	0.9	0.9
Participation in other studies	1.9	1.5	1.2	0.7	0.1
Unwillingness	12.2	8.1	5.5	4.4	4.3

AV = atrioventricular.

because of participation in other trials and unwillingness to participate in the MIAMI trial.

The randomized and excluded patients differed with regard to age and sex (Table III); the randomized patients were younger and more often men. Of those patients younger than 50, approximately 30% were randomized; less than 20% of those older than 70 were randomized. The proportion of patients with confirmed definite myocardial infarction according to the study criteria was higher among the randomized patients (74.1% vs 60.6%).

All but 74 patients fulfilled the entry age criteria of age <75. Only 4 of these were >75 years. Seventy-seven patients had heart rates ≤65 beats/min and 29 patients had systolic blood pressures ≤105 mm Hg.

Randomized patients: Data from the placebo and metoprolol groups with regard to age, sex, race and delay from onset of symptoms to injection are presented in Table IV. The mean age of the patients in the 2 groups was approximately 59 years, the majority of patients were white men and the 2 groups were evenly balanced with regard to basic demographic variables. In the 2 treatment groups the median delay in time between onset of symptoms and randomization was

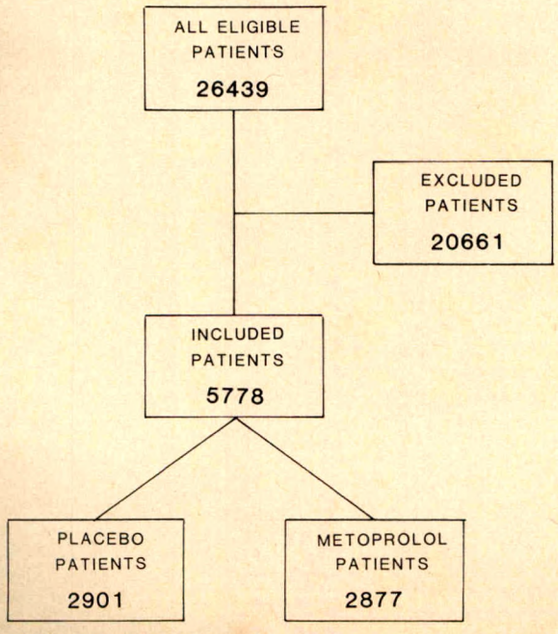

FIGURE 1. Patient recruitment flow chart.

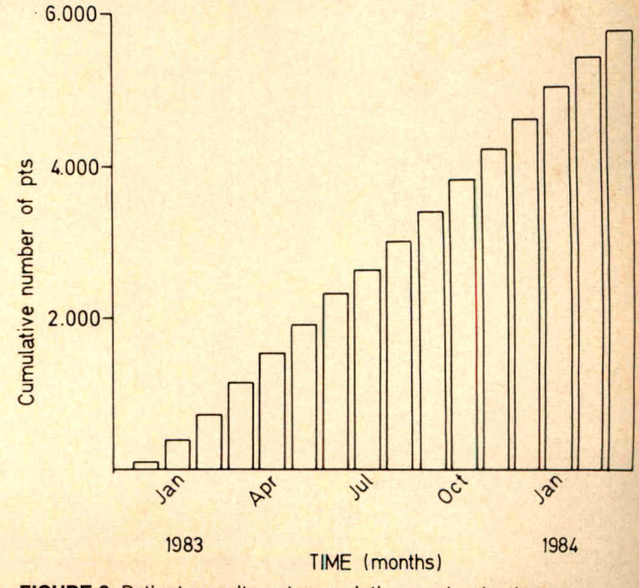

FIGURE 2. Patient recruitment, cumulative number by time.

TABLE III Comparison Between Randomized and Excluded Patients

	Randomized (n = 5,778) %	Excluded (n = 20,661) %	Eligible Patients Randomized %
Sex			
Male	77.6	74.1	23
Female	22.4	25.9	20
Definite MI	74.1	60.6	35
Age (years)			
<39	4.0	2.1	35
40–49	15.0	9.2	31
50–59	28.7	25.8	24
60–69	35.5	41.0	20
>70	16.8	21.8	18
Age (years)			
Mean ± SD	58.9 ± 10.1	61.4 ± 9.2	
Median	60.0	63.0	
Q_1	52.0	56.0	
Q_3	67.0	69.0	

MI = myocardial infarction; Q_1 = lowest quartile; Q_3 = highest quartile; SD = standard deviation.

approximately 6.7 hours; 25% of the patients were included within 4 hours and 75% of the patients within 12 hours. The median delay in time between onset of symptoms and admission to hospital was 3.3 hours. Previous clinical history and long-term pharmacologic treatment given before admission are presented in Table V.

Adminstration of drugs given after arrival in hospital but before randomization is presented in Table VI. The rates did not differ with respect to cardiac glycosides, diuretics and atropine.

Baseline heart rate, systolic blood pressure and frequencies of pulmonary rales, atrial fibrillation or flutter and ventricular fibrillation before randomization into the study are listed in Table VII. Mean heart rate for the 2 groups before randomization was 83 beats/min and mean systolic blood pressure was 141 mm Hg. Approximately 15% of patients presented with pulmonary rales; ventricular fibrillation before entry occurred in 2%.

Electrocardiograms classified before randomization are listed in Table VIII. Before randomization 20% of the patients had normal electrocardiograms; 70% could be classified as having signs of acute myocardial infarction; and 10% presented with other abnormalities. The predominant site of the acute myocardial infarction on presentation was the anterior wall.

The amount of trial medication injected in the 2 treatment groups is listed in Table IX. Between the evaluation of the patient and the actual injection, the ampoule was broken in 24 patients in the placebo and 15 patients in the metoprolol group but the patients deteriorated and the injections were not given. Almost all patients were injected with the full dose. A higher proportion of metoprolol patients did not tolerate the full 15 ml ($p < 0.001$). Most patients were also given the full initial oral dose 15 minutes after end of injection (Table X). More patients in the metoprolol group received reduced or no initial oral dosage ($p < 0.001$).

TABLE IV Baseline Characteristics. Demographic Data and Total Delay From Onset of Symptoms to Injection

	Placebo (n = 2,901)		Metoprolol (n= 2,877)	
	%	n	%	n
Age (years)				
<39	4.2	121	3.6	104
40–49	15.6	451	14.5	416
50–59	28.4	825	29.1	837
60–69	34.9	1,013	36.0	1,035
>70	16.9	491	16.9	485
Mean ± SD	58.8 ± 10.2		59.1 ± 9.9	
Median	60		60	
Q_1	52		52	
Q_3	67		67	
Sex				
Male	77.2	2,240	78.0	2,244
Female	22.8	661	22.0	633
Race				
White	95.4	2,768	96.1	2,765
Oriental	3.1	89	2.7	78
Black	0.5	13	0.2	7
Other	1.1	31	0.9	26
Delay time (hours)				
≤ 1	0.3	9	0.5	14
> 1 ≤ 3	12.6	365	12.5	359
> 3 ≤ 6	33.4	969	31.6	910
> 6 ≤ 9	17.7	512	20.5	590
> 9 ≤12	11.5	334	11.2	322
>12 ≤24	24.5	712	23.7	682
Mean ± SD		8.6 ± 6.0		8.6 ± 6.4
Median		6.5		6.8
Q_1		4.0		4.0
Q_3		12.0		11.5

Abbreviations as in Table III.

TABLE V Previous Clinical History and Long-Term Treatment Before Randomization

	Placebo (n = 2,901)		Metoprolol (n = 2,877)	
	%	n	%	n
Clinical history				
Previous myocardial infarction	16.1	467	16.0	459
Angina pectoris (>1 month)	29.5	855	27.7	798
Congestive heart failure	3.6	105	3.9	112
Atrial fibrillation/flutter	3.2	94	3.2	91
Chronic obstructive pulmonary disease	3.1	90	3.6	103
Hypertension	14.1	410	13.6	390
Diabetes	7.6	221	6.7	192
Bypass surgery	1.6	47	1.8	51
Smokers	52.1	1,509	50.6	1,457
Long-term treatment				
Cardiac glycosides	6.3	182	5.3	152
Diuretics	14.8	430	14.1	406
Antihypertensives	5.3	155	5.0	145
Lipid-lowering drugs	0.6	18	0.5	14
Anticoagulants	2.0	58	2.3	66
Antiarrhythmics	1.5	43	1.0	29

TABLE VI Treatment Given After Arrival in Hospital Before Randomization

	Placebo (n = 2,901)		Metoprolol (n = 2,877)	
	%	n	%	n
Cardiac glycosides	3.0	86	2.6	76
Diuretics	11.8	341	11.3	326
Atropine	2.1	61	1.5	44

After full intravenous dose, no or reduced oral doses were given to more patients in the metoprolol group ($p < 0.001$, Table XI).

Discussion

According to calculations based on the Göteborg Metoprolol Trial,[1] an inclusion rate of approximately 25% of eligible patients was expected. The observed rate was slightly lower. The relative frequencies of the exclusion criteria are difficult to compare with other studies and patient groups because they were coded according to a consecutive order. Thus the selection of the first criterion influences all rates of subsequent criteria.

The selection criteria in this study were not conventional. The aim was not to recruit all patients without contraindications to β blockade, but instead to focus

TABLE VII Clinical Findings After Admission to Hospital but Before Randomization

	Placebo (n = 2,901)		Metoprolol (n = 2,877)	
	%	n	%	n
Pulmonary rales	15.4	446	15.6	450
Atrial fibrillation/flutter	3.0	87	3.3	94
Ventricular fibrillation	2.2	64	1.7	50
Heart rate (beats/min)				
Mean ± SD		82.9 ± 13.9		82.5 ± 14.2
Q_1		72		72
Median		80		80
Q_3		90		90
Systolic blood pressure (mm Hg)				
Mean ± SD		141.1 ± 22.9		141.9 ± 23.1
Q_1		124		125
Median		140		140
Q_3		155		160

Abbreviations as in Table III.

TABLE VIII Signs on Electrocardiogram (ECG) and Localization of Suspected Myocardial Infarction (MI) Before Randomization

	Placebo		Metoprolol	
	%	n	%	n
ECG without pathologic changes	20.2	586	18.6	535
ECG pathologic but actual MI cannot be localized due to heart block, previous MI, etc.	10.2	297	10.5	301
Signs of actual MI	69.6	2,017	70.9	2,041
Anterior wall involvement	33.0	958	33.9	974
Inferior wall involvement	27.6	800	27.3	786
Other involvements	8.9	259	9.8	281
Pure anterior wall	24.7	715	25.3	727
Pure inferior wall	22.0	640	22.4	644
Missing		1		

TABLE IX Amount of Intravenous Dose Injected

	Placebo (n = 2,901)		Metoprolol (n = 2,877)	
	%	n	%	n
0 ml	0.8	24	0.5	15
5 ml	0.3	9	1.7	49
10 ml	0.5	15	3.0	85
15 ml	98.4	2,853	94.8	2,728

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TABLE X Initial Oral Dose 15 Minutes After Injection

	Placebo (n = 2,901)		Metoprolol (n = 2,877)	
	%	n	%	n
None	1.4	41	4.4	127
¼ tablet	1.0	28	4.6	133
½ tablet	97.6	2,832	91.0	2,617

on a subset of patients with a higher sympathetic activity, who were hypothesized to be at higher risk and more likely to benefit from metoprolol treatment. Consequently, of the excluded patients, 50% were excluded because they were receiving treatment with β blockers or calcium-channel blockers; another 25% did not have a high enough heart rate or systolic blood pressure; and another 13% had standard β-blocker contraindications.

It was not surprising, therefore, to find differences between the randomized and excluded patients with respect to age and sex distributions. It was somewhat remarkable, however, to observe a higher rate of confirmed infarctions among the randomized patients compared with excluded patients. It was also apparent that more contraindications to β blockade were found in higher age groups.

TABLE XI Initial Treatment. Reduced Trial Drug Administration

	Placebo (n = 2,901)		Metoprolol (n = 2,877)	
	%	n	%	n
Full intravenous–no oral dose	0.4	12	1.8	53
Full intravenous–reduced oral dose	0.5	15	2.5	71

The randomization procedure was effective in that the placebo and metoprolol groups appear well balanced regarding individual baseline variables of prognostic importance.

It can be concluded that, in accord with the study objectives, the randomized patients were not representative of all eligible patients and the treatment groups were well balanced at entry.

Reference

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Mortality

The MIAMI Trial Research Group

After 15 days there were 142 deaths in the placebo group (4.9%) and 123 deaths in the metoprolol group (4.3%), a difference of 13% (p = 0.29). The 95% confidence limits for the relative effect of metoprolol ranged from an 8% excess (−8%) to a 33% reduction (+33%) in mortality. There was generally a lower mortality rate for metoprolol-treated patients in most subgroups and a consistent tendency for a more pronounced difference between the treatment groups in those subgroups with a placebo mortality rate higher than the average for all placebo patients. Most deaths were cardiac and occurred among patients who developed a definite myocardial infarction (97%) and most of these had a Q-wave infarction (83%). Using a simple model, the placebo mortality was found to increase with increasing number of 8 risk predictors defined from prestudy experience, from 0% in patients with no risk predictors to 11.6% in patients with any 5 or more of these risk factors. Similarly, there was an increase in the difference between the treatment groups in favor of metoprolol with increasing number of placebo risk factors. Metoprolol had no apparent effect in a low-mortality risk group (≤2 risk factors), but there was a difference in mortality of 29% in favor of metoprolol in a high-risk group (≥3 risk factors) comprising one-third of the trial population. A multivariate model provided further evidence that the effect of metoprolol was not uniform among different risk categories based on clinical history and status at entry. There was no tendency for a significant drug effect in the low- and medium-risk classes. In the high-risk class constituting 23% of patients, however, there was an indication of a beneficial effect estimated as 39% reduction of mortality (95% confidence interval: +4 to +61%).

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During the last 2 decades a large number of randomized placebo-controlled trials have been performed using β blockers in the treatment of survivors of an acute myocardial infarction (AMI).[1] A beneficial effect on mortality by β blockade has been demonstrated mostly in late-entry studies with start of treatment 1 to several weeks after onset of infarction.[2,3] The total mortality reduction has averaged around 25%. It is now widely accepted that β blockade can improve long-term survival after AMI.

A smaller number of studies involved early start of treatment in AMI patients shortly after their arrival in a hospital.[4] The Göteborg Metoprolol Trial[5,6] showed a significantly lower total mortality in the treated group at the end of 3 months of follow-up.

The primary objective of the present trial was to evaluate further the effects of metoprolol on total mortality during the first 15 days after onset of suspected AMI. According to the protocol, subgroups were formed with respect to delay time, heart rate and suspected site of infarction at entry.

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Patients and Methods

All randomized patients were included. Information on the time, place (in or outside hospital), cause (cardiac or noncardiac) and mode of death was recorded.

Cardiac deaths were classified as end-stage left ventricular failure/congestive heart failure with or without lethal arrhythmias; primary lethal arrhythmias including ventricular fibrillation and asystole; sudden circulatory collapse; other; and unknown. Sudden circulatory collapse includes suspected or proven rupture of ventricular wall without observed arrhythmias or block. Among autopsied patients rupture of ventricular wall was recorded.

For descriptive purposes, mortality has also been examined in association with other outcome variables such as final diagnosis of and site of infarction (days 0 to 3). No statistical testing has been conducted on such associations.

Statistical analyses: The standard principles of statistical analyses[7] were applied. The mortality data from day 0 to day 15 have been analyzed on the "intention-to-treat" basis for all 5,778 patients randomized into the study.

Multivariate analyses were conducted to determine if the effect of metoprolol was dependent on baseline risk.[7] The study documented baseline variables known to be risk predictors of short- and long-term mortality rates.[8,9] These risk predictors have been considered in the multivariate analyses

TABLE I Total Mortality in Subgroups According to Clinical History

Group	% Mortality (no. of deaths/pts*) in Group: Placebo	Metoprolol	Difference† %
All Patients‡	4.9 (142/2,901)	4.3 (123/2,877)	13
Sex			
Men	4.5 (101/2,240)	4.2 (95/2,244)	6
Women	6.2 (41/661)	4.4 (28/633)	29
Age			
≤60 yrs (median)	1.8 (27/1,505)	1.9 (27/1,460)	−3
>60 yrs	8.2 (115/1,396)	6.8 (96/1,417)	18
Myocardial infarction			
Yes	7.7 (36/467)	4.6 (21/459)	41
No	4.3 (105/2,433)	4.2 (102/2,418)	2
Angina pectoris			
Yes	6.0 (51/855)	4.5 (36/798)	24
No	4.4 (90/2,045)	4.2 (87/2,079)	5
Congestive heart failure			
Yes	9.5 (10/105)	6.3 (7/112)	34
No	4.7 (131/2,795)	4.2 (116/2,765)	10
Hypertension			
Yes	7.6 (31/410)	4.9 (19/390)	36
No	4.4 (110/2,490)	4.2 (104/2,487)	5
Diabetes			
Yes	11.3 (25/221)	5.7 (11/192)	49
No	4.3 (116/2,679)	4.2 (112/2,685)	4
Smoking			
Yes	3.9 (59/1,509)	3.6 (52/1,457)	9
No	5.8 (81/1,390)	5.0 (71/1,420)	14

* For a few patients, some data on baseline characteristics were unavailable. Hence data in some subgroups do not equal total patients.

† % difference in mortality = (placebo mortality − metoprolol mortality) × 100/placebo mortality.

‡ Two patients in the placebo group were lost to 15 days' follow-up at the time the code was broken and were assumed to be alive in these calculations. One of these patients has subsequently been confirmed as alive.

aimed at determining how these baseline variables individually contribute to mortality risk in this patient sample and thus develop a mortality risk function from which an aggregate risk of dying within 15 days can be calculated for each patient. In developing this risk function, an assessment of whether specific risk predictors also influence the effect of metoprolol was also attempted. Two-tailed p values are given without any correction for multiple significance testing.

Two approaches were used. The first approach has been reported previously[10] and uses a risk function derived from 8 baseline variables: age >60 years (median), abnormal signs on electrocardiogram (ECG), history of myocardial infarction, hypertension, angina pectoris, congestive heart failure, diabetes, short- or long-term treatment with diuretics or cardiac glycosides. The mortality rate was examined in 6 risk groups in which patients had 0, 1, 2, 3, 4 and ≥5 of any of these risk factors. Two groups were formed retrospectively: a low-mortality risk group (≤2 risk factors) and a high-risk group (≥3 risk factors).

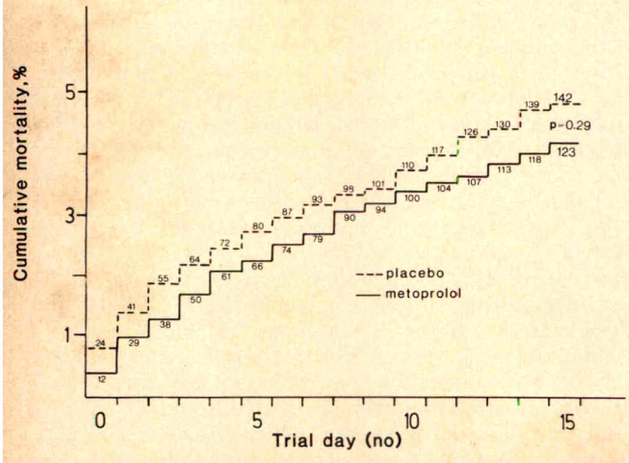

FIGURE 1. Cumulative percentage of mortality and number of deaths by time in the 2 treatment groups.

The second approach uses the logit model,[7,11] which is similar to a logistic regression model and enables the assessment of how the death risk varies with these risk predictors and if the effect of metoprolol varies with 1 or more of these predictors. The following 6 possible predictors of death risk were evaluated in a logit model for mortality within 15 days: age (3 classes, ≤54, 55 to 64 and ≥65 years), signs on ECG at entry (2 classes, normal and abnormal), risk group based on clinical history and status at entry (3 classes, low, medium and high), geographical region (3 classes, countries outside Europe, continental Europe and the United Kingdom, and Finland, Norway and Sweden), delay time (3 classes, <4, 4 to 8 and >8 hours) and drug (2 classes, placebo and metoprolol).

The clinical status variable of risk was defined as follows: high required that at least 1 of the risk indicators was present (history of myocardial infarction, congestive heart failure or diabetes); medium required that no indicator from the high-risk group was present but at least 1 of history of angina pectoris or hypertension, heart rate ≥90 beats/min or short-term treatment with diuretics in-hospital before randomization; and low required that no risk indicator belonging to the high and medium class was present.

The measure of death risk used in the logit model was the odds of death (the probability of death divided by the probability of survival).

TABLE II Total Mortality in Subgroups According to Long- or Short-Term Treatment Before Randomization

Group	% Mortality (no. of deaths/pts) in Group: Placebo	Metoprolol	Difference* %
Long-term			
Cardiac glycosides			
Yes	9.3 (17/182)	3.3 (5/152)	65
No	4.6 (124/2,718)	4.3 (117/2,724)	6
Diuretics			
Yes	7.4 (32/430)	4.4 (18/406)	40
No	4.4 (109/2,470)	4.2 (104/2,470)	5
Antihypertensives (other than diuretics)			
Yes	7.1 (11/155)	5.5 (8/145)	22
No	4.7 (130/2,745)	4.2 (114/2,731)	12
Antiarrhythmics			
Yes	7.0 (3/43)	3.5 (1/29)	—
No	4.8 (138/2,857)	4.1 (121/2,847)	12
Short-term (after admission)			
Cardiac glycosides			
Yes	4.7 (4/86)	2.6 (2/76)	—
No	4.9 (138/2,815)	4.3 (121/2,801)	12
Diuretics			
Yes	9.1 (31/341)	7.4 (24/326)	19
No	4.3 (111/2,560)	3.9 (99/2,551)	11
Atropine			
Yes	11.5 (7/61)	4.6 (2/44)	—
No	4.8 (135/2,840)	4.3 (121/2,833)	10

* % reduction in mortality (see Table I).

TABLE III Total Mortality in Subgroups in Relation to Clinical Status at Entry

Group	% Mortality (no. of deaths/pts) in Group: Placebo	Metoprolol	Difference* %
Pulmonary rales (≤10 cm)			
Yes	7.6 (34/446)	7.6 (34/450)	0
No	4.4 (108/2,455)	3.7 (89/2,427)	17
HR (beats/min)			
≤80†	4.3 (68/1,582)	3.4 (55/1,604)	20
>80	5.6 (74/1,319)	5.3 (68/1,273)	5
SBP (mm Hg)			
≤140†	4.9 (85/1,724)	4.3 (72/1,666)	12
>140	4.8 (57/1,177)	4.2 (51/1,211)	13
Signs on ECG			
Normal	0.9 (5/586)	0.9 (5/535)	—
Pathologic	3.7 (11/297)	2.3 (7/301)	38
Suspected AMI	6.2 (125/2,017)	5.4 (111/2,041)	13
Location of suspected AMI			
Anterior	8.2 (78/958)	7.0 (68/974)	15
Inferior	4.5 (36/800)	3.3 (26/786)	27
Others	4.3 (11/259)	6.0 (17/281)	−40
Delay time‡ (hours)			
≤6.7†	4.9 (72/1,477)	4.8 (68/1,415)	1§
>6.7	4.9 (70/1,424)	3.8 (55/1,462)	24§

* % reduction in mortality by metoprolol.
† Median.
‡ Time from onset of symptoms to blind injection.
§ Baseline variables predicting mortality not well balanced (delay time was not important in a multivariate analysis).
AMI = acute myocardial infarction; ECG = electrocardiogram; HR = heart rate; SBP = systolic blood pressure.

Results

After 15 days there were 142 deaths in the placebo group (4.9%) and 123 deaths in the metoprolol group (4.3%), a difference of 13% ($p = 0.29$). The 95% confidence limits of the relative effect of metoprolol ranged from an 8% excess (−8%) to a 33% reduction (+33%) in mortality. The cumulative mortality was always higher in the placebo group (Fig. 1).

Univariate analyses: Mortality was examined in relation to baseline variables (Tables I, II and III). Concerning the average effect in all patients, there was

TABLE IV Mortality in Subgroups in Relation to Final Infarct Diagnosis and Site Defined During Days 0 to 3

Group	No. of deaths (pts. in group) Placebo	Metoprolol
Myocardial infarction		
None	2 (639)	1 (635)
Possible	2(161)	2 (214)
Definite	137 (2,099)	120 (2,028)
Missing	1 (2)	
Non-Q-wave definite infarction	17 (537)	28 (565)
Q-wave definite infarction	120 (1,562)	92 (1,463)
Site of definite infarction		
Anterior	81 (981)	71 (978)
Inferior	36 (819)	30 (783)
Others	20 (299)	19 (267)

generally a lower mortality for metoprolol-treated patients in most subgroups. Further, there was a consistent tendency for a more pronounced difference between the treatment groups in those subgroups with a placebo mortality higher than the average for all placebo patients.

From information collected during study days 0 to 3, patients were diagnosed as having definite, possible or no AMI. Patients with definite AMI were classified into those with and without Q-wave infarction and according to site of definite AMI (Table IV). Most deaths occurred among patients who developed a definite AMI (97%) and most of these had a Q-wave infarction (83%).

Table V shows that most deaths occurred in the hospital and were cardiac. About half of the patients

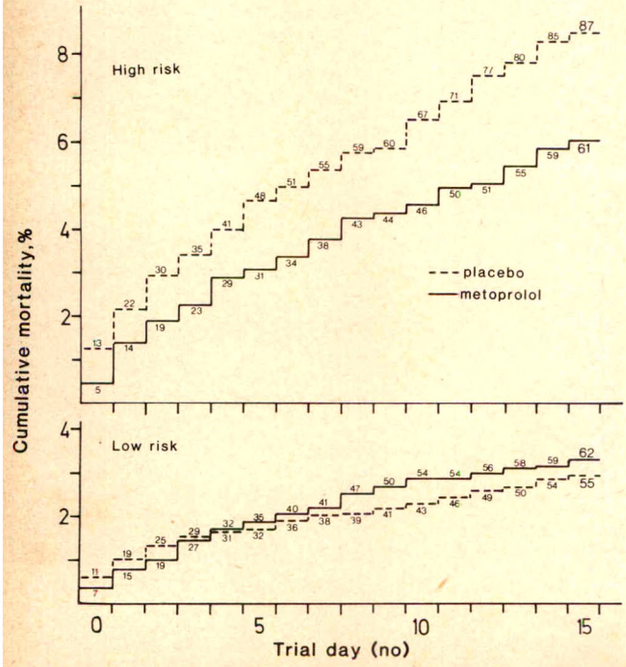

FIGURE 2. Cumulative percentage of mortality and number of deaths by time in the 2 treatment groups and according to risk group assignment (see Table VI).

TABLE V Classification of Deaths

Classification	No. of deaths (% in group of deaths) Placebo	Metoprolol
All deaths	n = 142	n = 123
Place of death		
In hospital	129 (91)	115 (93)
Out of hospital	13 (9)	8 (7)
Cause of death		
Cardiac	138 (97)	118 (96)
Noncardiac	4 (3)	5 (4)
All in-hospital deaths	n = 129	n = 115
Heart failure (LVF/CHF)		
Without arrhythmias	40 (31)	36 (32)
With arrhythmias*	29 (22)	27 (23)
Arrhythmias* or block without LVF/CHF	32 (25)	28 (24)
Sudden circulatory collapse†	21 (16)	19 (17)
Other	6 (5)	5 (4)
Unknown	1 (1)	0 (0)
Autopsy performed	n = 75‡	n = 67‡
Rupture of ventricular wall	39 (52)	32 (48)

* Lethal arrhythmias including ventricular fibrillation and asystole.
† The majority of patients were clinically judged to have a rupture of ventricular wall and most verified by autopsy.
‡ Autopsy was performed in 53 and 54% of all deaths in the placebo and metoprolol groups, respectively, often to verify suspected rupture.
CHF = congestive heart failure; LVF = left ventricular failure.

had heart failure and as many showed arrhythmias or block with or without concomitant heart failure. The proportion of such events in the treatment groups was very similar. Approximately 50% of the patients in both groups had signs of ventricular wall rupture on autopsy.

Analyses with a simple risk predictor: Using the simple model, the placebo mortality was found to increase with increasing number of the 8 risk predictors present (Table VI), from 0% in patients with no risk predictors to 11.6% in patients with any 5 or more of these risk factors. Similarly there was an increase in the difference between the treatment groups in favor of metoprolol with increasing number of risk factors. Baseline characteristics for the placebo- and metoprolol-treated groups were comparable within the low- (≤2 risk predictors) and high- (≥3 risk predictors) risk groups, respectively. Metoprolol had no apparent effect in the low-mortality risk group (95% confidence limits for the relative metoprolol effect −54 and +28%) but there was a difference in mortality of 29% (95% confidence limits +5 and +53%) in favor of metoprolol in the high-risk group (2,038 patients), constituting one-third of the trial population (Table VI, Fig. 2).

Multivariate analysis: In the logit model, the 4 predictors age, ECG, geographical region and risk had significant and independent effects on the odds for death. Delay time did not have a significant association with the risk of death nor was there a significant interaction between delay and the effect of metoprolol. Delay was therefore excluded from the model. Further analyses were based on the contingency table that included status (dead or alive), age, ECG, geographical region, risk and drug. In this model all predictors ex-

cept drug had a significant association with mortality risk ($p \leq 0.005$ for all) and the influence on the placebo patients is illustrated in Figure 3. The overall fit of the model was good ($p = 0.89$). Models including an interaction between drug and one of the other predictors were considered but only the interaction between drug and risk was non-negligible with a p value of 0.17. This interaction was not significant but the power of the interaction test is probably weak in the absence of a strong main drug effect. Because the interaction pattern with a more pronounced effect in the high-risk group (Fig. 4) seemed very reasonable, this interaction was investigated further. This logit model was tested against other similar models in which other interactions between drug and one of the other predictors were added and against models in which 1 predictor was deleted. These other interactions were weak and none of the alternative models gave a better fit to the observed data than the chosen model. There was a tendency for the drug effect to increase with increasing age, but this interaction was less pronounced than that with the risk group and so was not included in the model.

The logit analysis indicates that the uncertainty about the effect of metoprolol on the risk of death is large and that the effect is perhaps not uniform in the different risk classes (Fig. 4). The 95% confidence intervals for the difference in the death risk between placebo- and metoprolol-treated patients are −63 to +40% for the low-risk group, −56 to +29% for the medium-risk group and +4 to +61% for the high-risk group. These are nominal 95% confidence limits without correction for multiple comparisons. The high-risk group consisted of 23% of all randomized patients and 40% of the placebo deaths. The possibility of a strong beneficial effect of metoprolol in the high-risk group was further investigated by examining the *observed* death rates. Figures 5 and 6 show the observed death rates in the different age classes and in the different geographic regions, respectively, among patients with abnormal signs on ECG and belonging to the high-risk class. In the high-risk class, metoprolol mortality was lower than placebo mortality in all 3 age classes and throughout the 3 geographic regions. There is consistency within the data for the high-risk class. When the data were broken down simultaneously according to age and geographic region for patients in the high-risk class, metoprolol-treated patients showed a lower mortality than placebo-treated patients in all 9 cells except 1 in which they were equal (Fig. 7).

TABLE VI Total Mortality in All Patients in Various Mortality Risk Groups Defined from Baseline Risk Predictors*

No. of Risk Predictors Present	% mortality (no. of deaths/pts) in Group: Placebo	Metoprolol	Difference† %
0	0.0 (0/259)	0.0 (0/207)	0
1	1.4 (11/790)	1.8 (15/820)	−32
2	5.3 (44/825)	5.6 (47/839)	− 5
3	6.4 (31/482)	5.6 (27/486)	14
4	9.1 (26/286)	7.0 (21/302)	24
≥5	11.6 (30/259)	5.8 (13/223)	50
≤2 (low risk)	2.9 (55/1,874)	3.3 (62/1,866)	−13
≥3 (high risk)	8.5 (87/1,027)	6.0 (61/1,011)	29

* The 8 risk predictors were: age >60 years (median); abnormal ECG at entry; history of myocardial infarction, angina pectoris, congestive heart failure, hypertension or diabetes; long- or short-term treatment with diuretics or cardiac glycosides before randomization.
† % difference in mortality (see Table I).

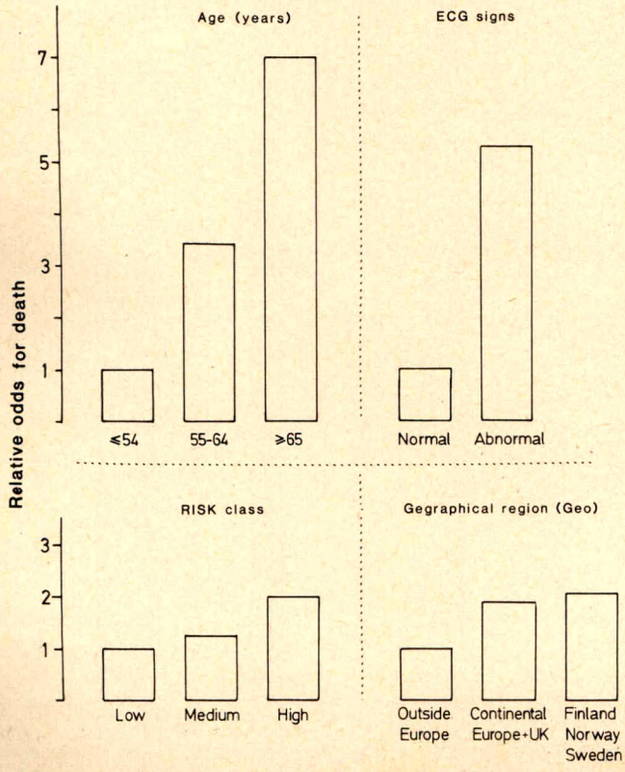

FIGURE 3. Logit analysis of mortality. Relative odds for death by categories of age, signs on electrocardiogram (ECG), risk class and geographic regions.

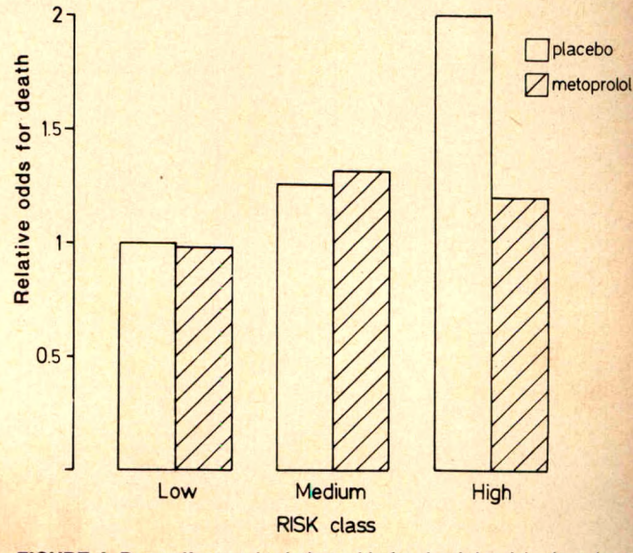

FIGURE 4. Drug effect and relative odds for death by risk class (see text).

Discussion

The MIAMI trial was designed to study the effect of early intervention with metoprolol in a selected group of suspected AMI patients having a predicted placebo mortality rate of 7% after 15 days. The sample size was calculated to detect a difference of 35% in mortality between the 2 treatment groups with a power of 90% (2-sided, $p < 0.05$). The project protocol allowed for an increase in the sample size if the total mortality was lower than assumed after 2,000 patients were entered. The final placebo mortality rate (4.9%), however, was still lower than anticipated. Clearly, a considerable proportion of the randomized patients were low-risk patients who had been legitimately included according to the selection criteria. This may explain why the observed difference in mortality between treatment groups (13%) was less than expected and not statistically significant (95% confidence interval −8 to +33%). A trial of 15,000 to 20,000 patients would be required to obtain statistical significance for a difference of 13% with a placebo mortality rate of 5%.

In a recent review,[4] the pooled results (from 4,555 patients) given early treatment with intravenous and oral β blocker showed a 1-week mortality rate of 4.7% in control subjects compared with 4.3% for the β-blocker group, a difference of about 10%. From that pooled data, the upper 95% confidence limit was reported to be compatible with a 33% reduction in the odds of death; thus, it is in close agreement with the confidence limit of the MIAMI trial. In a recently published early intervention study of metoprolol in 800 patients from Belfast,[12] no significant difference in the in-hospital mortality rate was found between the placebo and metoprolol group, 5.2 vs 6.0%, respectively, with 95% confidence limits of −81 and +51%.

With a simple method, risk categories were defined using the unweighted combination of 8 risk predictors. With the presence of increasing numbers of risk predictors, the placebo mortality increased as did the difference between the death rates of the treatment groups. It appears that the study patients are composed of patients with a broad spectrum of mortality risk; most are at low risk that seems unaltered by metoprolol treatment after 15 days. It should be noted that the very high-mortality-risk patients were not included in this trial because the severity of their cardiovascular complications contraindicated treatment with a β blocker.

A multivariate analysis was necessary to quantitate the individual contribution of the risk predictors and to assess whether metoprolol's effect was influenced by these predictors.

It is likely that marked variations in mortality between centers and between countries will be found in a large multicenter trial. From the logit model it was found that geographic region had importance for prediction of mortality in addition to age, abnormalities on ECG and risk class based upon clinical history and status at entry. The lowest mortality was found outside Europe (Australia, New Zealand, Canada and Southeast Asia), while in Europe, Finland, Norway and Sweden had slightly higher odds for death than the rest of continental Europe and the United Kingdom.

The need to include geographic status to account for regional variations in mortality most likely indicates

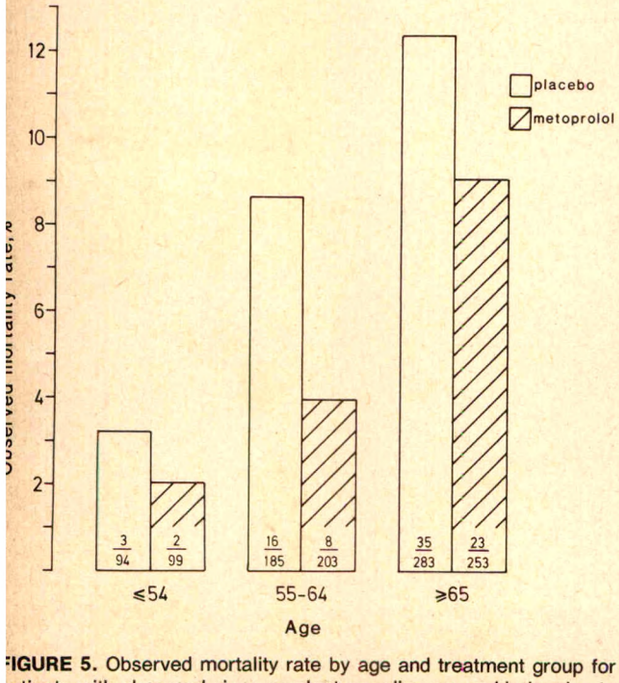

FIGURE 5. Observed mortality rate by age and treatment group for patients with abnormal signs on electrocardiogram and belonging to the high-risk class (see text).

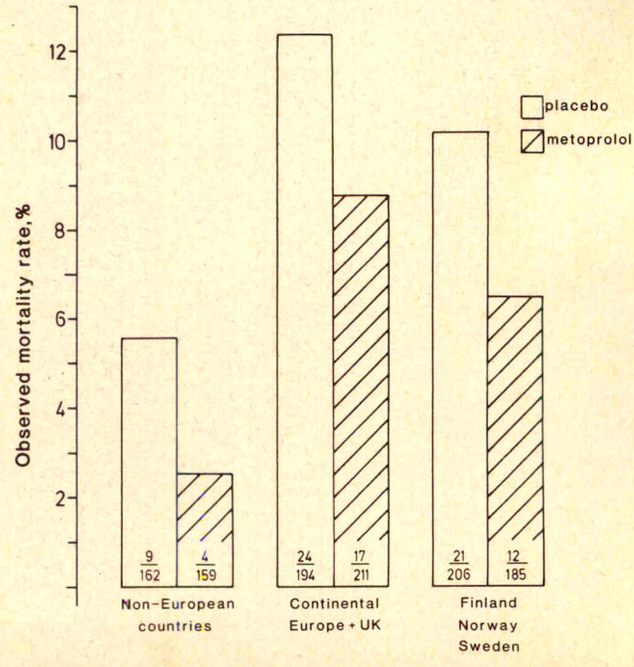

FIGURE 6. Observed mortality rate by geographic region and treatment group for patients with abnormal signs on electrocardiogram and belonging to the high-risk class (see text).

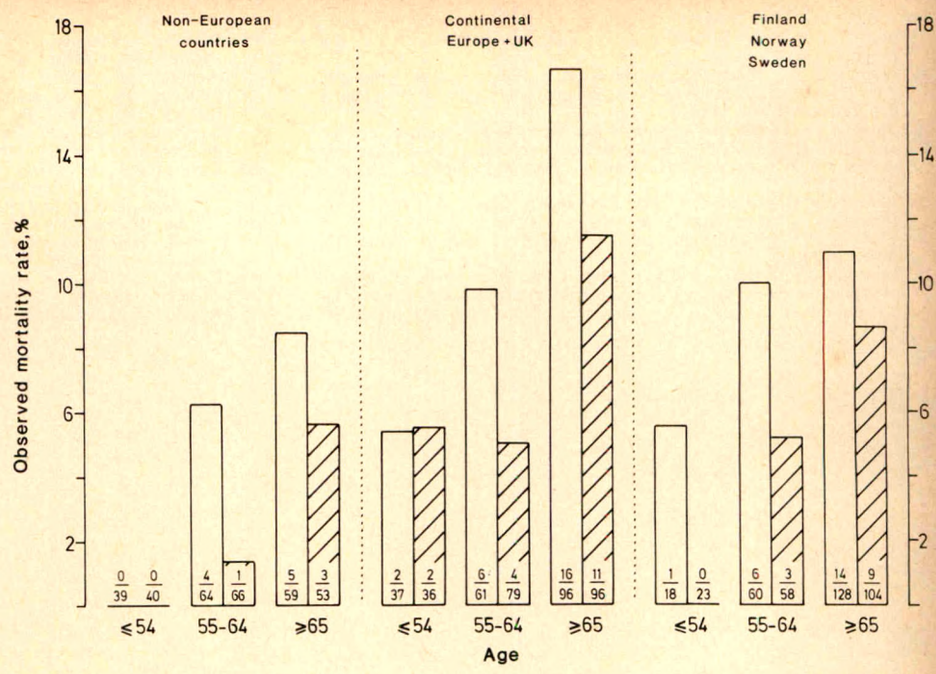

FIGURE 7. Observed mortality rate by age, geographic region and treatment group for patients with abnormal signs on electrocardiogram and belonging to the high-risk class (see text). □ = placebo; ▨ = metoprolol.

variations in patient selection between centers and regions that have not been adequately described by the baseline characteristics included in the model. This possibility will be explored further by examining the mortality among excluded patients in some representative centers.

The main indication from the logit model was that the effect of metoprolol was perhaps not uniform among the different risk classes defined from the patients' clinical history and status at entry. The observed difference in mortality in favor of metoprolol in the high-risk group was independent of age, signs on ECG at entry and geographic location of the patient. These findings are also consistent with results from other studies.

A beneficial effect among patients older than 60 to 65 has been observed for metoprolol in an early-intervention study[5,6] and for timolol, propranolol and metoprolol in late-intervention studies.[13–15] On the other hand, a tendency toward an increased mortality in patients older than 65 treated with β blockers has been suggested from an early-intervention study with alprenolol[16] and a late-entry study with oxprenolol.[17] The evidence from the present study—that patients with a history of cardiovascular disease or diabetes were at higher risk and achieved greater benefit—is in keeping with similar observations in other β-blocker postinfarction studies.[2,6,15,18,19]

The data from the MIAMI patient population obviously indicate a considerable heterogeneity in the distribution of baseline risk factors and associated mortality outcome. It is likely that this may be mainly explained by differences among centers in selection of trial patients.

One method of assessing the reproducibility of the previous Göteborg Metoprolol Trial would be to compare the patients of the 3 hospitals common to the 2 studies. The patients selected with MIAMI entry criteria from the Göteborg Metoprolol Trial showed a 7.0% placebo and a 3.8% metoprolol mortality rate after 15 days, a 45% difference (unpublished data). Similar results were obtained for all MIAMI patients recruited at these 3 hospitals: 9.9% placebo and 4.0% metoprolol mortality rates, a difference of 60%. The results obtained in these 3 hospitals were thus very similar in the 2 trials; they are also similar to those in the high-risk patients in the MIAMI trial.

It appears that early intervention with metoprolol in suspected myocardial infarction can achieve an early reduction in mortality, the magnitude of which is dependent upon the average death risk of the patient group.

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Development of Myocardial Infarction

The MIAMI Trial Research Group

The effect of metoprolol on the development of an acute myocardial infarction (AMI) during days 0 to 3 and on late first and recurrent infarctions during days 4 to 15 has been investigated. Signs on electrocardiogram (ECG) were well balanced between the treatment groups at entry; 70% of patients had signs of suspected AMI and 19% of patients had normal ECGs. The remaining patients had abnormal ECGs but actual infarction could not be localized. The localization of suspected AMI was equivalently distributed in the 2 groups before randomization. Metoprolol altered the distribution of patients diagnosed during days 0 to 3 as having definite, possible or no AMI ($p < 0.02$). In the placebo group, there were more patients with definite AMI (72.5% vs 70.5%) and less with possible AMI (5.6% vs 7.4%) than in the metoprolol group. A larger proportion of patients developed a Q-wave infarction during days 0 to 3 in the placebo group (53.9%) compared with the metoprolol group (50.9%, $p = 0.024$). No difference in the effect of metoprolol regarding localization of the early AMI was observed. Late first myocardial infarction development (days 4 to 15) was observed in 20 patients (0.7%) in each group. Recurrent myocardial infarction tended to develop more frequently during days 4 to 15 in the placebo group compared with the metoprolol group (3.9% vs 3.0%, $p = 0.08$). In a multivariate analysis, delay time between onset of symptoms and randomization, signs on ECG at entry and metoprolol treatment were found to have a significant effect on the development of an AMI during days 0 to 3. Additionally, the delay time significantly influenced this effect of metoprolol. Metoprolol was found to decrease the risk of a definite AMI for patients treated early, while almost no effect was seen in patients treated more than 8 hours after onset of pain. In patients randomized early, the incidence of early AMI was particularly lowered in the metoprolol group among patients with heart rate, systolic blood pressure and rate pressure product higher than the median.

(Am J Cardiol 1985;56:23G–26G)

Upon hospital admission many patients with symptoms of acute myocardial infarction (AMI) have not yet developed clear-cut abnormalities on the electrocardiogram (ECG). A proportion of these patients may have arrived relatively early in the course of their infarction. Therefore, an appropriate intervention applied very soon after hospital arrival might prevent the infarct development.

The objectives of the present trial were to assess the incidence of definite AMI within 3 days, the incidence of late first myocardial infarction and recurrent myocardial infarction during the remaining trial period and the incidence of definite myocardial infarction during 5 and 15 days in patients with and without signs of infarction on the admission ECG. According to the protocol, subgroups were formed with respect to delay between onset of pain and blind injection, heart rate and suspected site of infarction before randomization.

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Patients and Methods

The data from all randomized patients were analyzed. The diagnosis of infarction during days 0 to 3 was recorded as well as the type of diagnostic evidence and the site of infarction. The occurrence of a late first infarction or a recurrent infarction during days 4 to 5 and days 6 to 15 was also documented.[1]

Signs of AMI on ECG before randomization, including ST elevation, T-wave inversion or Q waves, were used to document the localization of myocardial infarction before trial injection in the same way as for the final diagnosis. The absence of all pathologic changes on ECG was noted as was the presence of pathologic changes, e.g., heart block and previous myocardial infarction, preventing further ECG classification. In addition to the subgroup analyses stated in the protocol, a number of subgroups were formed based on systolic blood pressure, rate-pressure product, pulmonary rales before trial injection, age and clinical history (previous myocardial infarction, angina pectoris and hypertension).

The general principles of statistical analysis were followed and have been described in a previous article in this issue.[1]

TABLE I Electrocardiogram (ECG) Findings of Suspected Acute Myocardial Infarction (AMI) Before Randomization

	Placebo		Metoprolol	
	%	n	%	n
ECG without pathologic changes	20.2	586	18.6	535
ECG pathologic but actual myocardial infarction cannot be localized due to heart block, previous myocardial infarction, etc.	10.2	297	10.5	301
Signs of suspected AMI	69.6	2,017	70.9	2,041
Anterior wall involvement	33.0	958	33.9	974
Inferior wall involvement	27.6	800	27.3	786
Other involvements	8.9	259	9.8	281
Pure anterior wall	24.7	715	25.3	727
Pure inferior wall	22.0	640	22.4	644
Missing		1		

TABLE II Acute Myocardial Infarction (AMI) During Days 0 to 3

	Placebo		Metoprolol	
	%	n	%	n
No AMI	22.0	639	22.1	635
Possible AMI	5.6	161	7.4	214
Definite AMI	72.5	2,099	70.5	2,028
Missing		2		

Results

Signs of suspected AMI on ECG before randomization were observed in 69.5% of the patients in the placebo group versus 70.9% in the metoprolol group. A similar proportion of patients in both groups (10.2% vs 10.5%) had an ECG with pathologic signs but actual infarction could not be localized. The localization of ECG abnormalities was equivalently distributed in the 2 groups before randomization (Table I).

Early acute myocardial infarction (days 0 to 3): The distribution of definite and possible AMI differed in the 2 groups ($p < 0.02$). In the placebo group the patients had more definite and less possible AMI than patients in the metoprolol group (Table II).

A larger proportion of patients developed a Q-wave infarction in the placebo group compared with the metoprolol group (53.9% vs 50.9%, $p = 0.024$, Table III). No difference regarding localization of the early AMI was observed.

Late first and recurrent myocardial infarction (days 4 to 15): Late first myocardial infarction development (days 4 to 15) was observed in 20 patients (0.7%) in each group. Recurrent myocardial infarction tended to develop more frequently during days 4 to 15 in the placebo group compared with the metoprolol group (3.9 vs 3.0%, $p = 0.08$).

Definite myocardial infarction (days 0 to 5 and days 0 to 15): During the first 5 days 72.6% of the patients in the placebo group versus 70.7% in the metoprolol group developed a definite myocardial infarction ($p = 0.12$). The number of patients developing myocardial infarction during days 0 to 15 was 73% versus 71.2% ($p = 0.12$, Table IV).

TABLE III Type and Site of Definite Acute Myocardial Infarction During Days 0 to 3

	Placebo		Metoprolol	
	%	n	%	n
Q wave	53.9	1,562	50.9	1,463
Non–Q wave	18.5	537	19.6	565
Anterior wall involvement	33.8	981	34.0	978
Inferior wall involvement	28.3	819	27.2	783
Other involvements	10.3	299	9.3	267
Pure anterior wall	22.8	661	22.6	650
Pure inferior wall	21.4	620	20.1	579

TABLE IV Definite Myocardial Infarctions During Different Time Periods

	Placebo		Metoprolol	
	%	n	%	n
Days 0 to 5	72.6	2,106	70.7	2,035
Days 6 to 15	2.8	78	1.9	52
Days 0 to 15*	73.0	2,119	71.2	2,048

* A few patients developed myocardial infarctions on days 0 to 5 as well as days 6 to 15.

In patients with signs of suspected AMI on ECG before randomization, 88.4% in the placebo group compared with 84.4% in the metoprolol group developed myocardial infarction during days 0 to 5 ($p = 0.002$). Corresponding values for days 0 to 15 were 88.9% versus 85.6% ($p = 0.002$).

In patients without signs of suspected AMI on ECG before randomization, 30.4% in the placebo group compared with 26.5% in the metoprolol group developed myocardial infarction during the first 5 days ($p = 0.16$). Corresponding values for days 0 to 15 were 31.7% and 27.7%, respectively ($p = 0.14$).

Early acute myocardial infarction—univariate analysis: The incidence of definite AMI during days 0 to 3 was reduced by metoprolol treatment in patients randomized early after onset of symptoms, with higher entry heart rate, systolic blood pressure and rate-pressure product and signs of suspected AMI on ECG before randomization (Table V). A higher incidence of AMI was observed in the placebo group compared with the metoprolol group in the elderly (Table V). There was no indication that previous myocardial infarction, previous angina pectoris or previous hypertension were of importance.

In patients randomized within the median delay time, the incidence of early AMI was particularly lowered in the metoprolol group among patients with heart rate, systolic blood pressure and rate pressure product higher than the median (Table VI).

Early acute myocardial infarction—multivariate analysis: The possible predictors of development of a definite AMI within 3 days after blind injection were: infarct localization at entry ECG (anterior, inferior, other, pathologic and normal); delay from onset of pain to blind injection (<4, 4 to 8 and >8 hours); heart rate (<80, 80 to 90 and >90 beats/min); and drug (placebo and metoprolol). All these predictors except

TABLE V Acute Myocardial Infarction (AMI) During Days 0 to 3: Prerandomization Variables

	Placebo		Metoprolol	
	%	n	%	n
Per protocol subgroups				
Delay time				
≤ median	74.0	1,094	70.1	992
> median	70.6	1,005	70.9	1,036
Heart rate before blind injection				
≤ median	69.5	1,099	68.6	1,100
> median	75.8	1,000	72.9	928
Signs of AMI on ECG before blind injection				
None	29.9	175	25.8	138
Pathologic, but localization not possible	46.1	137	49.5	149
Suspected AMI	88.6	1,787	85.3	1,741
Anterior	89.9	861	85.2	830
Inferior	91.6	733	90.8	714
Others	74.5	193	70.1	197
Retrospectively formed subgroups				
Systolic blood pressure before blind injection				
≤ median	69.8	1,203	70.4	1,173
> median	76.1	896	70.6	855
Rate-pressure product before blind injection				
≤ median	69.1	1,028	69.3	984
> median	75.8	1,071	71.6	1,044
Age				
≤ median	68.1	1,025	68.1	994
> median	76.9	1,074	73.0	1,034

heart rate were found to have significant effects on the odds for a definite AMI.

Metoprolol decreased the risk of a definite AMI for patients treated early, while almost no effect was seen for patients treated >8 hours after onset of pain ($p = 0.02$ for the test of interaction between drug and delay time; $p = 0.01$ for the test including both main drug effect and drug interaction with delay time). The risk for an AMI varied with signs at entry ECG (Table VII), but there was no significant interaction between the effect of metoprolol and ECG signs at entry.

Discussion

In most patients admitted to a coronary care unit with a strong suspicion of AMI, the infarction process has already started when they are regarded as suitable for intervention. In many patients Q waves appear within the first 2 hours after onset of symptoms.[2,3] However, for other patients there is a longer interval until abnormalities appear on the ECG.

TABLE VI Acute Myocardial Infarction During Days 0 to 3 in Patients Randomized Within the Median Delay Time (7 hours)

	Placebo		Metoprolol	
	%	n	%	n
Heart rate before blind injection				
≤ median	71.4	603	69.5	557
> median	77.6	491	70.7	435
Systolic blood pressure before blind injection				
≤ median	71.6	595	69.5	548
> median	77.1	499	70.7	444
Rate-pressure product before blind injection				
≤ median	70.6	531	69.5	483
> median	77.6	563	70.6	509

Propranolol given to patients with threatening AMI without changes on ECG within 4 hours of onset of pain resulted in fewer completed infarctions.[4] Similar results have been reported for atenolol.[5]

In the Göteborg Metoprolol Trial there was no effect on the development of confirmed early AMI in all patients. In a retrospective subgroup analysis, the patients given metoprolol within 12 hours after the onset of pain and with a heart rate >70 beats/min before start of treatment were partly protected against development of AMI.[6]

Speculations regarding a protective role of long-term β blockade against the development of myocardial infarction were first reported in 1973.[7,8] In several trials evaluating the effect of long-term β blockade after myocardial infarction it has been shown that chronic β blockade reduces the incidence of nonfatal reinfarction.[9–13] In the Göteborg Metoprolol Trial, fewer patients developed a late myocardial infarction in the metoprolol group.[14] In other studies, no difference between treatment groups was detected.[15,16]

The present results indicate that metoprolol treatment may have transferred definite to possible AMI,

TABLE VII Observed Rates of Patients With Definite Acute Myocardial Infarction (AMI) Within 3 Days After Randomization and Expected Rates According to the Logit Model

		Signs on Electrocardiogram (ECG) Before Randomization									
Delay Time (hours)		Normal		Pathologic but Localization of AMI Not Possible		ECG Indicating Anterior AMI		ECG Indicating Inferior AMI		ECG Indicating Other AMI Localization	
		P	M	P	M	P	M	P	M	P	M
<4	observed	30.7	19.3	44.8	52.9	94.0	85.1	93.4	92.3	75.4	65.5
	expected	32.9	24.7	54.2	44.2	90.1	85.9	93.1	90.0	77.2	69.4
4–8	observed	32.4	27.0	50.0	41.7	90.6	86.1	93.1	90.7	69.7	67.3
	expected	32.3	25.0	52.4	44.6	89.4	86.1	92.6	90.1	76.0	69.7
>8	observed	26.5	28.3	43.4	55.1	87.1	84.7	89.2	90.0	77.0	74.6
	expected	26.3	27.1	46.3	47.4	86.9	87.4	90.7	91.1	71.2	72.1

M = metoprolol; P = placebo.

and similarly Q-wave to non–Q-wave myocardial infarction. Consequently it seems that treatment with metoprolol protected some patients from developing a definite Q-wave AMI.

The results from the univariate analyses are consistent with those of the previous study: patients with a high initial rate-pressure product were at greater risk of developing AMI, and metoprolol treatment had a more pronounced effect in these patients. Also, age seemed to be important to the results. However, when further evaluating the results in a multivariate model, delay from onset of symptoms to start of treatment was found to be the most important determinant of the protective effect of metoprolol against infarct development. The effect is mainly restricted to patients given the treatment <8 hours after onset of pain, and the most pronounced differences were observed in those patients with normal signs on ECG at entry—a group that constituted only 20% of the study sample.

The reduction in the number of Q-wave infarctions is in agreement with the concept of infarct size limitation. Recent studies also suggest that Q-wave infarctions have more complications and a worse prognosis than non–Q-wave infarctions.[17,18]

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Enzymatic Estimation of Infarct Size

The MIAMI Trial Research Group

The maximum serum activity for aspartate aminotransferase (s-ASAT) during the first 3 days was recorded in 5,507 patients with suspected or definite acute myocardial infarction. The s-ASAT activity was corrected for the normal range from each center. The median s-ASAT activity was 4.9 arbitrary units in the placebo group versus 4.6 arbitrary units in the metoprolol group ($p = 0.072$). Univariate analyses indicated that the delay time between onset of symptoms and randomization and sympathetic activity at entry significantly influenced the effect of metoprolol. A similar decrease in serum enzyme activity after metoprolol treatment was observed independent of signs of infarct localization on the entry electrocardiogram.

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The estimated infarct size is a major determinant for morbidity and mortality in acute myocardial infarction (AMI).[1–4] Different methods for assessing infarct size are available; they include analyses of serum enzyme activity,[5] precordial electrocardiographic mapping,[6] vectorcardiography[7] and radionuclide methods.[8] All these methods have disadvantages and none of them exactly reflects the infarct size. The maximum serum activity of enzymes, however, has been shown to quite closely reflect the size and the severity of the infarction.[1–4,9–11]

This article will describe the effect of metoprolol on serum enzyme activity. According to the protocol, subgroups were formed with respect to delay time, heart rate and site of suspected infarction at entry.

Patients and Methods

All patients in whom any of the enzymes used for infarct size estimation was analyzed were included in this study.

Blood samples were requested to be drawn according to local practice or at least once a day for days 0 to 3 to determine serum enzyme activity. It was requested that all centers should measure serum aspartate aminotransferase (s-ASAT) activity. The case report form allowed for recording of maximum assay results of s-ASAT, s-LD (lactate dehydrogenase), s-LD1 (isoenzyme 1), s-CK (creatine kinase), s-CK MB and s-CK B. Data were recorded as either international units/liter or μkat/liter. A factor of 60 was used to convert μkat/liter to international units. Because routine local methods were used for enzyme analyses, great differences in numerical values of the enzyme activities were expected, mainly owing to different reaction temperatures (25 to 37°C). The upper and lower limits of the normal range for each enzyme were recorded in all centers. Enzyme activity was therefore transformed to a corrected value (arbitrary unit, [a.u.]). A linear correction was obtained by dividing the difference of the individual serum activity and the midpoint of the local normal range by the midpoint of the local normal range.

Because s-ASAT was the enzyme analyzed in almost all centers, this article will mainly deal with this enzyme. Overall results will also be reported for the other enzymes, with exceptions for LD and LD1, which were studied in a subgroup of patients in an optional study and will be reported elsewhere.

In addition to the subgroup analyses stated in the protocol, a number of subgroups were formed based on systolic blood pressure, rate-pressure product, pulmonary rales, age and clinical history (myocardial infarction, angina pectoris and hypertension).

Statistical analyses: The general principles of statistical analysis were followed. Because only maximum serum activity was documented, it was considered inappropriate to conduct a detailed multivariate analysis to assess the influence of various baseline variables on the effect of metoprolol. Instead, pertinent subgroups are presented for descriptive purposes.

Results

Maximum serum activity for s-ASAT was recorded in 95% of patients with suspected or definite AMI. Corresponding figures for s-CK, s-CK MB and s-CK B were 75%, 20% and 14%, respectively. A lower median serum enzyme activity was observed in the metoprolol

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TABLE I Maximum Serum Enzyme Activities in All Patients

		Placebo			Metoprolol		
	n	Q_1	Median	Q_3	Q_1	Median	Q_3
s-ASAT	5,507	0.9	4.9	11.0	0.8	4.6	10.3
s-CK	4,329	0.9	7.2	18.3	0.8	7.0	17.2
s-CKMB	1,144	1.0	8.6	23.5	0.9	7.4	19.6
s-CKB	806	2.0	9.0	18.9	2.0	8.0	18.5

Q_1 = lower quartile; Q_3 = upper quartile.

TABLE II Maximum s-ASAT Activity in Relation to Delay Between Onset of Symptoms and Randomization, Heart Rate (HR), Systolic Blood Pressure (SBP) and Rate-Pressure Product (RPP) Before Blind Injection

		Placebo	Metoprolol
Subgroup*	n	Median a.u.	Median a.u.
Delay time ≤7 hrs	2,786	5.3	4.7
Delay time >7 hrs	2,721	4.4	4.4
HR ≤80 beats/min	3,048	4.1	4.2
HR >80 beats/min	2,459	5.9	5.2
SBP ≤140 mm Hg	3,209	4.4	4.8
SBP >140 mm Hg	2,298	5.3	4.2
RPP ≤11,200	2,766	4.1	4.4
RPP >11,200	2,741	5.9	4.7

* Dichotomized by the median.
a.u. = arbitrary unit.

TABLE III Maximum s-ASAT Activity in Patients Randomized Within the Median Delay Time in Relation to Heart Rate (HR), Systolic Blood Pressure (SBP) and Rate-Pressure Product (RPP) Before Blind Injection

		Placebo	Metoprolol
Subgroup*	n	Median a.u.	Median a.u.
HR ≤80 beats/min	1,586	4.7	4.6
HR >80 beats/min	1,200	6.0	5.0
SBP ≤140 mm Hg	1,554	4.9	4.9
SBP >140 mm Hg	1,232	5.9	4.7
RPP ≤11,200	1,391	4.3	4.8
RPP >11,200	1,395	6.2	4.7

* Dichotomized by the median.
a.u. = arbitrary units.

TABLE IV Maximum s-ASAT Activity in Relation to Findings on Electrocardiogram (ECG) Before Blind Injection

		Placebo	Metoprolol
ECG Before Blind Injection	n	Median a.u.	Median a.u.
No signs of AMI	1,090	0.6	0.6
Signs of AMI	3,835	7.4	6.8
Anterior AMI	1,824	7.8	7.5
Inferior AMI	1,498	7.8	6.8
Other AMI	513	5.0	4.0
Pure anterior AMI	1,360	7.3	6.7
Pure inferior AMI	1,212	7.8	6.6

AMI = acute myocardial infarction; a.u. = arbitrary unit.

group compared with placebo for all enzymes (Table I). The median s-ASAT activity was 4.9 a.u. in the placebo group versus 4.6 a.u. in the metoprolol group ($p = 0.072$).

In patients entered within the median delay time (7 hours), the reduction in serum enzyme activity after metoprolol treatment was more substantial ($p = 0.026$, Table II).

Among all randomized patients initial heart rate did not appear to have a pronounced influence on the effect of metoprolol treatment on s-ASAT activity ($p = 0.12$, Table II). In patients with a systolic blood pressure higher than the median (140 mm Hg), s-ASAT activity was lower in the metoprolol group compared with the placebo group ($p < 0.001$, Table II). In patients with a rate-pressure product higher than the median before randomization, s-ASAT activity was higher in the placebo group compared with the metoprolol group ($p < 0.001$, Table II).

Among patients randomized within the median delay time (7 hours) and with heart rate, systolic blood pressure or rate-pressure product higher than the median at entry, enzyme activity after metoprolol treatment was significantly decreased compared with placebo ($p = 0.026$, $p = 0.005$ and $p < 0.001$, respectively, Table III).

In patients with signs of suspected AMI on electrocardiogram before randomization, s-ASAT activity was higher in the placebo group compared with the metoprolol group ($p < 0.001$, Table IV). A similar decrease in serum enzyme activity after metoprolol treatment was observed independent of infarct localization before randomization (Table IV).

Among patients who developed definite AMI, s-ASAT activity tended to be higher in the placebo group compared with the metoprolol group ($p = 0.10$, Table V).

In patients older than the median age, the serum enzyme activity was higher (5.4 a.u.) in the placebo group compared with the metoprolol group (4.7 a.u., $p < 0.010$).

Discussion

The hypothesis that β blockade may limit indexes of infarct size in man has been tested. Intravenous β blockers given early in the course of AMI have resulted in a reduction of ST-segment elevation and relief of chest pain.[12–14] In later, large, randomized trials β blockade given within a few hours after the onset of pain has consistently lowered serum enzyme activity;[15–21] in contrast, treatment started later has had no effect.[15–17,20] In some studies, independent electrocardiographic registrations have supported these findings.[17,18] In a recent propranolol study in AMI, no reduction in infarct size was detected perhaps because too few patients were included early.[22] In that same study[22] there was a tendency for a positive effect of propranolol in patients treated within 8 hours of onset of symptoms of AMI.

TABLE V Maximum s-ASAT Activity in Relation to Final Acute Myocardial Infarction (AMI) Diagnosis Days 0 to 3

		Placebo	Metoprolol
	n	Median a.u.	Median a.u.
No AMI	1,233	0.3	0.3
Possible AMI	360	0.4	0.6
Definite AMI	3,914	7.8	7.4

a.u.= arbitrary unit.

Different enzyme analyses were performed in the MIAMI trial according to the local practice in each center. In 95% of all participating patients, the maximum activity of s-ASAT was recorded and, therefore, all results in the various subgroup analyses performed have been presented for this enzyme. One major disadvantage of using s-ASAT activity as an indirect measurement of infarct size is its lack of specificity. This might have underestimated the true effect of metoprolol. The reduction in serum enzyme activity, expressed in percentage, seemed to be higher when more heart-specific enzymes such as s-CK MB or s-CK B were analyzed.

The findings of this study are compatible with other studies, even though the overall effect on serum enzyme activity in all patients lacked pronounced statistical significance. They are also compatible with the findings of a study on infarct development,[23] in which delay time had an important influence on the effect of metoprolol. The reduction in serum enzyme activity appeared to be restricted to patients treated shortly after the onset of suspected infarction.

In the previously reported Göteborg Metoprolol Trial[24] the prerandomization heart rate and rate-pressure product were of importance. These findings were corroborated in this study. In addition the present study showed a reduction in serum enzyme activity in patients with a high systolic blood pressure.

The better reduction of serum enzyme activity among patients with signs of infarction on the electrocardiogram at the time of randomization might be explained by several factors. In the group of patients with no signs of AMI on ECG there were probably several patients with no ischemic heart disease. In the present study, infarct localization did not appear to influence the effect of metoprolol on enzyme levels.

When the present results are considered and related to our previous report[17] and reports from other groups,[15,16,18] it must be concluded that early treatment with metoprolol limits enzymatically estimated infarct size and that the magnitude of this effect is strongly influenced by the time between onset of symptoms and start of treatment.

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Narcotic Analgesics and Other Antianginal Drugs

The MIAMI Trial Research Group

The effect of metoprolol on chest pain has been assessed in terms of the duration and the use of narcotic analgesics, nitrates and calcium-channel blockers. Fewer metoprolol-treated patients in the MIAMI trial were given narcotic analgesics (49% of the placebo patients vs 44% of the metoprolol patients, $p < 0.001$), nitrates (55% vs 53%, $p = 0.10$) and calcium-channel blockers (12% vs 9%, $p < 0.001$). A total number of 6,697 dose equivalents of narcotic analgesics were given to the placebo group compared with 5,493 dose equivalents to the metoprolol group, a difference of 18% ($p < 0.001$). Mean dose equivalents were 2.3 and 1.9, respectively. The analysis of the total use of the 3 types of treatment for ischemic chest pain showed a significantly less frequent use of treatment for chest pain in the metoprolol group than in the placebo group ($p < 0.004$). The relative difference in the incidence of drug treatment tended to be more striking for patients with maximal therapy, i.e., receiving high doses of narcotic analgesics, nitrates and calcium-channel blockers. There were 22% fewer patients receiving 4 or more doses of narcotic analgesics in the metoprolol group than in the placebo group. A multivariate analysis disclosed that site of suspected infarction, delay time, entry systolic blood pressure and metoprolol treatment all had a significant effect on the use of narcotic analgesics. There was a nonsignificant tendency for heart rate to be of importance. In the placebo group the use of narcotic analgesics increased with decreasing delay time and increasing systolic blood pressure. The use was highest for patients with signs of anterior infarction on electrocardiogram (ECG) and lowest for patients with normal ECG at entry. The effect of metoprolol was independent of delay time and systolic blood pressure but varied with ECG classification. The highest effect was seen among patients with signs of anterior infarction.

(Am J Cardiol 1985;56:30G–34G)

A variety of pharmacologic and other measures have been used to control chest pain in acute myocardial infarction (AMI) ranging from analgesics or tranquilizers[1] to drugs that act mainly through direct or indirect effect on the ischemic myocardium.[2] Persistent or recurrent chest pain may induce adverse systemic and coronary circulatory effects via autonomic reflexes, mediated via sympathetic efferent nerves,[3] but also to some degree via the vagal nerve.[4]

In order to relieve pain, very large doses of morphine-like drugs are sometimes required that may themselves induce unfavorable effects.[5–7] Additional approaches to pain control in AMI are therefore desirable. Earlier studies have suggested the beneficial effect of metoprolol both in prevention of ischemic chest pain and treatment of pain.[8–10]

The aim of the present analysis was to assess the effect of metoprolol compared with placebo on chest pain as reflected by the duration of treatment with narcotic analgesics, use of analgesics, nitrates and calcium-channel blockers. According to the protocol, subgroups were formed with respect to delay time, heart rate and site of infarction.

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Patients and Methods

All patients (n = 5,778) were included in the analysis. Pain as such was not measured directly. Instead, the usage and number of doses of narcotic analgesics were used as markers of chest pain, as well as the use of nitrates and calcium-channel blockers. One dose equivalent of any narcotic analgesic was defined as the dose equipotent to the analgesic effect of 5 mg of morphine. The duration of pain was defined as the time in hours from randomization to the time of injection of the last dose of narcotic analgesic. This could only be measured during days 0 to 5.

In addition to the subgroup analyses stated in the protocol, a number of subgroups were formed based on systolic blood pressure, rate-pressure product, age, sex, diuretic usage and heart failure.

Statistical methods: The general principles of statistical analysis were followed.[11]

A univariate analysis was performed to see whether there was any influence of the variables defining the subgroups on the use of narcotic analgesics.

An analysis was undertaken of the effect of metoprolol on the combined use of nitrates, calcium-channel blockers and single and multiple doses of narcotic analgesics. Narcotic analgesics were considered the strongest and 3 levels were used (no analgesics, 1 to 3 dose equivalents of analgesics and 4 or more dose equivalents of analgesics). Because nitrates could be and were used freely during the entire trial period, calcium-channel blockers were considered "stronger" than nitrates (drug given or not given). Nitrates were ranked lowest and 2 levels were again used (given or not given). Consequently, 12 classes were constructed to describe different strengths of antianginal and analgesic treatment and perhaps reflect different degrees of ischemic chest pain. In this analysis, the distribution of patients over the 12 classes is described graphically in the 2 treatment groups, and the difference between the treatment groups in these distributions was tested.[12] A difference in the distribution between treatment groups would reflect a difference in the combined use of antianginal drugs and hence may suggest an effect on chest pain by metoprolol.

In addition a multivariate model was applied to analyze the importance of different factors for the development of chest pain requiring treatment with narcotic analgesics.

In a logit model, the influence of the following factors on the odds that a patient will be treated with a narcotic analgesic during days 0 to 15 was analyzed: electrocardiogram (ECG) on admission (anterior infarction, inferior infarction, other locations, pathologic but localization not possible and no abnormalities), delay time from onset of chest pain to randomization (<4, 4 to 8 and >8 hours), heart rate (<80, 80 to 90 and >90 beats/min), systolic blood pressure on admission (<140, 140 to 160 and >160 mm Hg) and drug (placebo or metoprolol).

Results

Narcotic analgesics were given to 49.4% of the patients in the placebo group compared with 44.1% in the metoprolol group, a difference of 11% ($p < 0.001$). Nitrates were given to 55.3% in the placebo group compared with 53.1% in the metoprolol group ($p = 0.10$). Calcium-channel blockers were used more often in the placebo group (11.8%) than in the metoprolol group (8.8%), a difference of 25% ($p < 0.001$, Fig. 1).

The total number of dose equivalents of narcotic analgesics during days 0 to 15 differed by 18% ($p < 0.001$) between the placebo group ($n = 6,697$) and the metoprolol group ($n = 5,493$). A mean of 2.31 dose equivalents/patient was given to the placebo group compared with 1.91 in the metoprolol group during days 0 to 15 ($p < 0.001$).

Among patients to whom narcotic analgesics had actually been given during days 0 to 15, the mean dose equivalents were 4.69 in the placebo compared with 4.32 in the metoprolol group, a difference of 8% ($p = 0.05$).

The total pain duration differed by 17% ($p < 0.001$) between the placebo group (42,935 hours) and the metoprolol group (35,675 hours). Mean duration of pain for the placebo group was 14.8 hours compared with 12.4 hours for the metoprolol group ($p < 0.001$). When only the patients who had received narcotic analgesics were analyzed, no difference in mean pain duration was found; it was 30.8 hours for the placebo group compared with 29.2 hours for the metoprolol group ($p < 0.2$).

Among patients with entry heart rates higher than the median (80 beats/min), narcotic analgesics were given to 52.2% in the placebo group compared with 43.9% in the metoprolol group, a difference of 16% ($p < 0.001$, Fig. 2) and the mean dose equivalents in the placebo group were 2.51 compared with 2.0 in the metoprolol group, a difference of 20% ($p < 0.001$, Fig. 3).

For patients with entry systolic blood pressure higher than the median (140 mm Hg) the percentage use of narcotic analgesics was 54% in the placebo group compared with 44.8% in the metoprolol group, a difference of 17% ($p < 0.01$, Fig. 2) and the mean dose equivalents were 2.64 and 2.0, respectively, a difference of 24% ($p < 0.001$, Fig. 3).

The influence of rate-pressure product on the use of narcotic analgesics revealed a similar pattern in the 2 treatment groups.

In all the remaining subgroups of patients in whom entry heart rate, systolic blood pressure or rate-pressure product was lower than the median, there was a consistently less pronounced and nonsignificant difference in favor of metoprolol between the treatment groups for all variables (Fig. 2 and 3).

Neither age, sex nor acute heart failure on admission, defined as administration of diuretics before randomization, had any association with the use of narcotic analgesics.

The analysis of the total use of the 3 types of treatment for ischemic chest pain showed a significantly different distribution in the 2 treatment groups ($p < 0.004$). The difference in the percentage use of drug

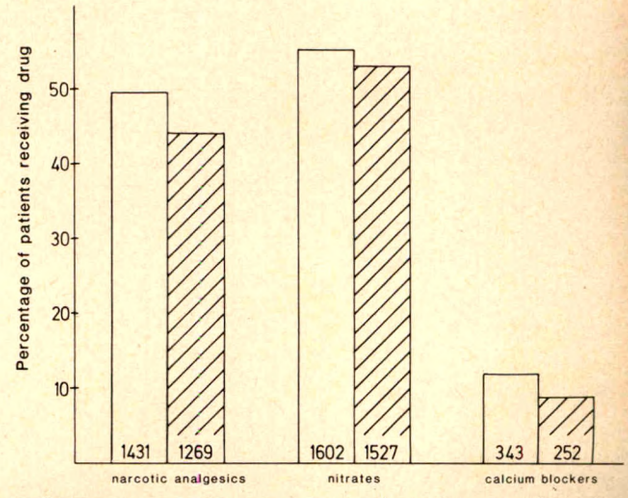

FIGURE 1. Number and percentage of patients given narcotic analgesics, nitrates and calcium-channel blockers during days 0 to 15. □ = placebo patients; ▨ = metoprolol patients.

treatment tended to be more pronounced for patients with maximal therapy, i.e., those receiving high doses of narcotic analgesics, nitrates and calcium-channel blockers. Although this was only a small group, 42% fewer patients received the maximal treatment in the metoprolol group compared with placebo (Fig. 4). The difference for all patients receiving 4 or more doses of narcotic analgesics, constituting one-fourth of all placebo patients, was 22%. Thus, patients who seem to benefit most from metoprolol are those who suffered the most pain, as reflected by the high use of narcotic analgesics with or without combined treatment with nitrates and calcium-channel blockers.

The multivariate analysis disclosed that site of infarction, delay time and systolic blood pressure had a significant effect on the use of narcotic analgesics. There was a nonsignificant tendency for heart rate to be of importance.

In the placebo group the use of narcotic analgesics increased with decreasing delay time and increasing systolic blood pressure. Furthermore, the use was most frequent for patients with signs of anterior infarction on ECG and lowest for patients with normal ECG.

The drug effect did not vary significantly with delay time and systolic blood pressure, but varied significantly with ECG classification at entry. The highest effect was seen among patients with signs of anterior infarction. For patients with signs on ECG classified as "inferior", "pathological" or "normal", only a minor drug effect was observed (Table I).

Discussion

The present MIAMI trial confirmed previous findings of a reduced use of narcotic analgesics in the early

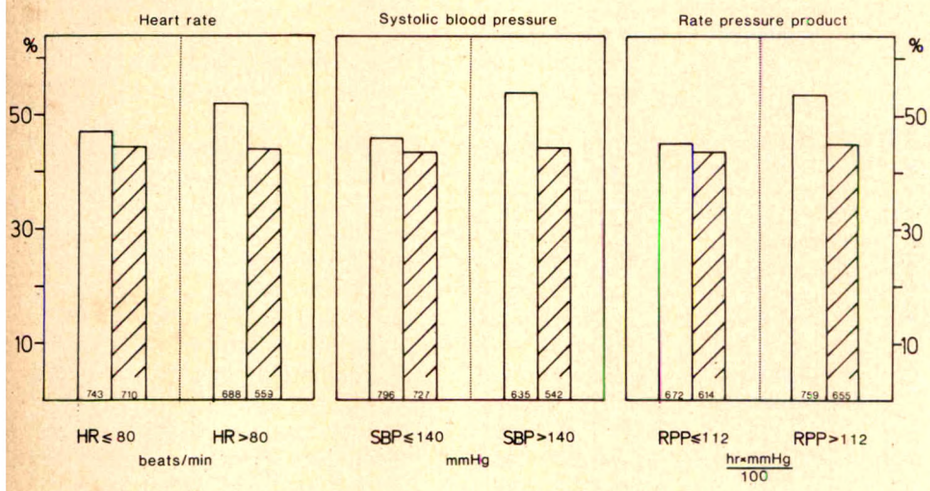

FIGURE 2. Number and percentage of patients receiving narcotic analgesics during days 0 to 15 among those having entry heart rate (HR), systolic blood pressure (SBP) and rate-pressure product (RPP) below and above median values, respectively. □ = placebo patients; ▨ = metoprolol patients.

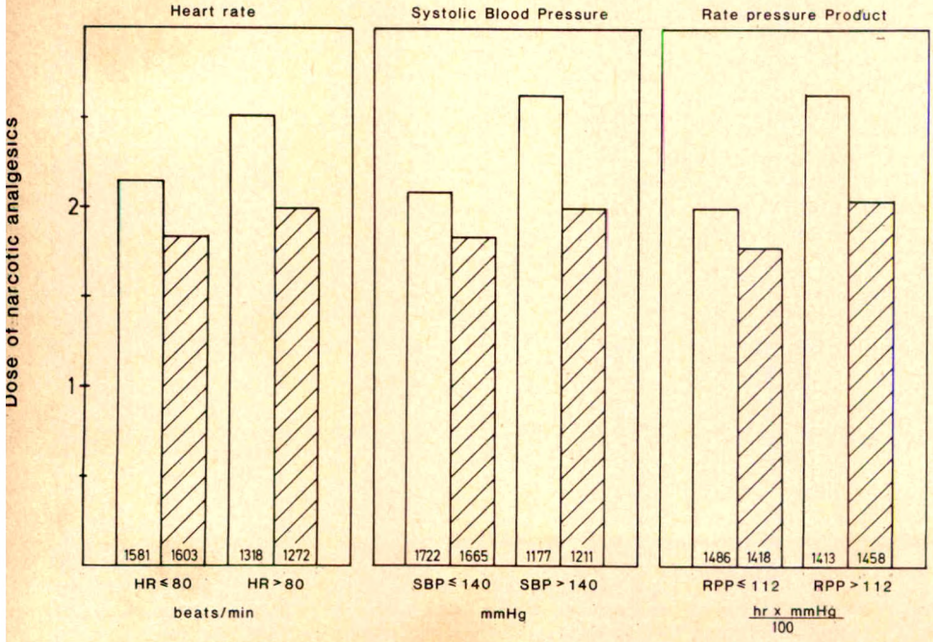

FIGURE 3. Mean dose of narcotic analgesics during days 0 to 15 among those having entry heart rate (HR), systolic blood pressure (SBP), and rate-pressure product (RPP) below and above median values, respectively. □ = placebo patients; ▨ = metoprolol patients.

TABLE I Estimated Expected Proportions of Patients (%) Given Narcotic Analgesics, According to the Logit Model

SBP (mm Hg)	Delay (hours)	Signs on Electrocardiogram (ECG) of Site of Suspected Infarction at Entry									
		Anterior		Inferior		Others		Abnormal ECG		Normal ECG	
		P	M	P	M	P	M	P	M	P	M
<140	<4	68.6	56.6	57.3	56.3	55.2	48.7	45.1	42.0	36.1	34.7
	4–8	64.0	51.5	52.2	51.2	50.0	43.6	40.1	37.1	31.5	30.2
	>8	53.3	42.5	43.2	42.2	41.1	35.0	31.7	29.0	24.2	23.1
140–160	<4	70.2	58.5	59.1	58.2	57.0	50.6	47.0	43.8	37.8	36.4
	4–8	65.7	53.4	54.1	53.1	51.9	45.5	41.9	38.8	33.2	31.8
	>8	57.1	44.4	45.0	44.0	42.9	36.7	33.4	30.6	25.6	24.5
>160	<4	72.7	61.5	62.2	61.2	60.1	53.8	50.1	46.9	40.9	39.4
	4–8	68.5	56.5	57.2	56.2	55.1	48.7	45.0	41.9	36.0	34.6
	>8	60.2	47.5	48.2	47.2	46.0	39.7	36.3	33.4	28.1	26.9

M = metoprolol; P = placebo; SBP = systolic blood pressure.

phase of myocardial infarction after treatment with metoprolol.[9,10]

Although incidence and intensity of pain were not directly measured in the present trial, the amount of analgesics and the time span over which they were given undoubtedly reflect the intensity and duration of ischemic chest pain. The fact that a positive effect on chest pain could be detected even though more than half of the placebo patients were given nitrates is important because nitrates have been shown to be effective for pain control in AMI.[13] In fact there was a trend to less use of nitrates, as well as a significant reduction in the use of calcium-channel blockers, in the metoprolol group. This reflects a reduction in the incidence of a low degree of pain for which these drugs are used. The decreased usage of narcotic analgesics in the metoprolol group indicates that recurrent chest pain was prevented. The lower mean dose of narcotic analgesics among those patients receiving analgesics also indicates that pain intensity may have been reduced by metoprolol.

In patients with acute heart failure a worsening of chest pain may have been anticipated after metoprolol, as further dilatation of the ventricle may increase myocardial oxygen consumption. The effect of increase in wall tension on myocardial oxygen consumption may, however, have been counteracted by the pronounced reduction in rate-pressure product. Therefore, there is no support from the present trial for the proposal that AMI patients with chest pain and mild heart failure should be treated with nitrates in preference to metoprolol. Patients with high heart rate and blood pressure at entry seemed to respond more favorably than those with low heart rate and blood pressure. However, a selection of patients with heart rate >65 beats/min for the trial may have obscured the true importance of heart rate. An interesting finding is that heart rate does not seem to be a strong determinant of the drug effect according to the multivariate analysis. The more pronounced benefit in patients with anterior infarction may be due to the fact that they seem to have more pain (higher usage of narcotic analgesics) (Table I) and to have higher heart rates compared with those with inferior infarction. The analysis does not exclude the possibility that metoprolol might be effective in patients with inferior infarction and high heart rates.

Metoprolol was effective in patients admitted with short as well as long delay after onset of chest pain, even though the intensity of chest pain was more pronounced in patients arriving early (Table I). Metoprolol seems to be of special value for pain control in patients with severe and prolonged pain. It also seems that metoprolol has a pain-relieving effect additional to nitrates and calcium-channel blockers.

The additional effect of metoprolol in patients given nitrates may be because nitrates mainly affect blood pressure. An increase in heart rate may occur after treatment with nitrates in patients with left-sided heart failure.[13,14] Similar effects are seen after calcium-channel blockers.[15,16] Reduction of blood pressure is therefore common for all 3 drugs; a fall in heart rate is only seen after metoprolol.

Prevention and reduction of chest pain in patients with AMI or impending infarction seem to be parallel

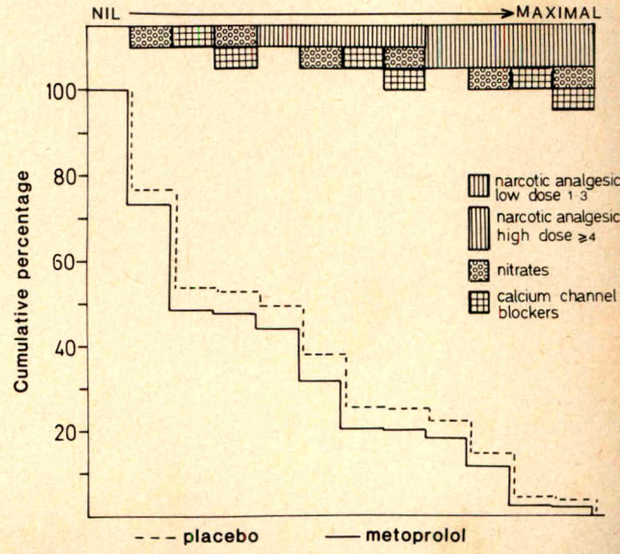

FIGURE 4. Cumulative distribution curve of combined treatment with narcotic analgesics, nitrates and calcium-channel blockers in all patients during days 0 to 15.

to prevention of infarct development[17] and reduction of indexes of size of infarction.[18] Pain abolition may be mediated through common pathways.

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Arrhythmias

The MIAMI Trial Research Group

Forty-five patients in the placebo (1.5%) and 29 in the metoprolol (1%) groups, respectively, were receiving antiarrhythmic drugs on a long-term basis before entry into the trial. Before randomization, 2.2% (n = 64) of the placebo and 1.7% (n = 50) of the metoprolol patients developed ventricular fibrillation (VF) in the hospital. The corresponding figures for atrial fibrillation or flutter were 3% (n = 87) and 3.3% (n = 94). After randomization, there was no significant difference in the number of patients who developed VF in the placebo (n = 52) and the metoprolol (n = 48) groups. The total number of episodes of VF tended to be fewer in the metoprolol group (n = 67) compared with the placebo group (n = 96). The tendency was, however, not apparent until after 5 days. When the occurence of VF was related to high- and low-mortality risk groups, any beneficial effect of metoprolol was confined mainly to the high-risk group. A similar proportion of patients underwent electric conversion for ventricular tachyarrhythmia in the 2 groups. Although antiarrhythmic drugs were intended to be given only for major ventricular tachyarrhythmias a large proportion of patients received such treatment. Significantly more patients were treated with antiarrhythmics in the placebo (21.5%) than in the metoprolol group (19.2%, p = 0.03) during the study period, but predominantly during the first 5 days. Atrial fibrillation or flutter and other supraventricular tachyarrhythmias were significantly less frequent in the metoprolol than in the placebo group, as was the use of cardiac glycosides. The sum of patients who had a nonfatal VF or who died during days 0 to 5 was not different between the treatment groups.

(Am J Cardiol 1985;56:35G–38G)

The introduction of coronary care units has decreased mortality in acute myocardial infarction (AMI) largely because of effective treatment of ventricular fibrillation (VF) and prophylaxis against VF and prolonged attacks of ventricular tachycardia (VT) as well as other arrhythmias.

One of the secondary objectives of the MIAMI trial was to assess the effect of metoprolol on VF. Besides VF other types of tachyarrhythmias and bradyarrhythmias were also studied. The influence of metoprolol on the occurrence of these arrhythmias is reported in this article.

According to the protocol the aim was to study the incidence of VF together with the sum of deaths and nonfatal VF during the first 5 days in the placebo and metoprolol groups. Further, the occurence of VT, atrioventricular block, atrial fibrillation and other supraventricular tachycardia and the use of digitalis and antiarrhythmic agents are reported.

Patients and Methods

All randomized patients were included. In patients with VF, the date and time of each episode were recorded. Before breaking the trial code, episodes of VF obviously induced by such iatrogenic procedures as cardiac catheterization and open-heart surgery were omitted from the analysis. Similarly, agonal VF, defined as VF in association with refractory cardiogenic shock or pulmonary edema, was not included in the analysis. Consequently, the analysis includes both patients with primary and secondary VF, but it was not possible to separate these 2 types.

Ventricular tachycardia: The MIAMI manual of procedures recommended that VT should be treated immediately if it markedly influenced hemodynamics or caused symptoms but otherwise only if it was sustained for more than 30 seconds. DC conversion was always to be performed initially for rapid treatment of VT and VF. Thereafter treatment with lidocaine was suggested. The drug was to be administered according to a dosage schedule outlined in the manual of procedures (75 mg intravenously as a bolus dose followed by intravenous infusion of 4 mg/min during 3 hours. Thereafter the infusion rate should be reduced to 2 to 3 mg/min). It was suggested that ventricular ectopic beats were not to be treated unless they caused signs of impaired cardiac function, e.g., hypotension or heart failure, or if they caused subjective discomfort. It was recommended that all other antiarrhythmic agents should be avoided.

Supraventricular arrhythmias: Two categories were recorded, atrial fibrillation or flutter and other supraventricular tachycardia (rate exceeding 120 beats/min). The last category could be either an ectopic supraventricular tachycardia or a sinus tachycardia.

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Atrioventricular blocks and asystole: First-degree atrioventricular block was recorded when the conduction time exceeded 0.26 seconds and asystole was defined as asystole necessitating treatment.

Antiarrhythmic agents: The use of cardiac glycosides and antiarrhythmic drugs was recorded for days 0 to 5 and 6 to 15 of the trial period.

The MIAMI manual of procedures contained advice concerning treatment. Digitalis was recommended for supraventricular tachyarrhythmias if the ventricular rate exceeded 120 beats/min or if there were frequent atrial ectopics or recurrent atrial fibrillation or flutter. DC conversion was to be used when indicated. According to local practice, verapamil could be cautiously given intravenously and orally in patients without heart failure. The use of digitalis was not separated according to whether this drug had been used for heart failure or tachyarrhythmia. It was recommended that digitalis be avoided for the treatment of heart failure in patients with sinus rhythm. It was suggested that other antiarrhythmic agents be restricted only to symptomatically or hemodynamically important supraventricular or ventricular arrhythmias or after VF.

Results

Forty-five patients in the placebo (1.5%) and 29 in the metoprolol (1%) groups were on long-term therapy with antiarrhythmic drugs before entry into the trial. Before randomization 2.2% (n = 64) of the placebo and 1.7% (n = 50) of the metoprolol patients developed in-hospital VF. The corresponding figures for atrial fibrillation or flutter were 3% (n = 87) and 3.3% (n = 94). The median delay time between onset of symptoms and randomization in both groups was between 6 and 7 hours and the mean delay time was 8.6 hours.

Ventricular fibrillation and tachycardia: VF was reported in 132 patients. In 2 of these patients it was iatrogenically induced and in 30 patients, only agonal episodes were noted. These 32 patients were excluded from the analysis. Thus, the remaining number of patients with VF was 100; of these, 52 (1.8%) belonged to the placebo and 48 (1.7%) to the metoprolol group (Fig. 1). The total number of episodes of VF was somewhat lower in the metoprolol group (n = 67) compared with the placebo group (n = 96), but this difference was not significant statistically and the tendency was only apparent during days 6 to 15. During this time period 54 episodes of VF occurred in the placebo group and 24 in the metoprolol group (Fig. 2).

Both the number of patients with VF and total number of episodes of VF have been analyzed for low- and high-risk patients defined in Table VI in a previous article in this issue.[1] Among the low-risk patients there was no difference between the treatment groups; a tendency towards a lower number of episodes of VF was apparent among high-risk patients in the metoprolol compared with the placebo group (Fig. 3). The patients on a full dose of metoprolol tended to have a lower incidence of VF compared with placebo (Fig. 4).

Electrically converted VT occurred among 1.4% (n = 40) of the placebo and 1.3% (n = 37) of the metoprolol patients (Table I).

Deaths and nonfatal ventricular fibrillation, days 0 to 5: The number of patients who died or had a

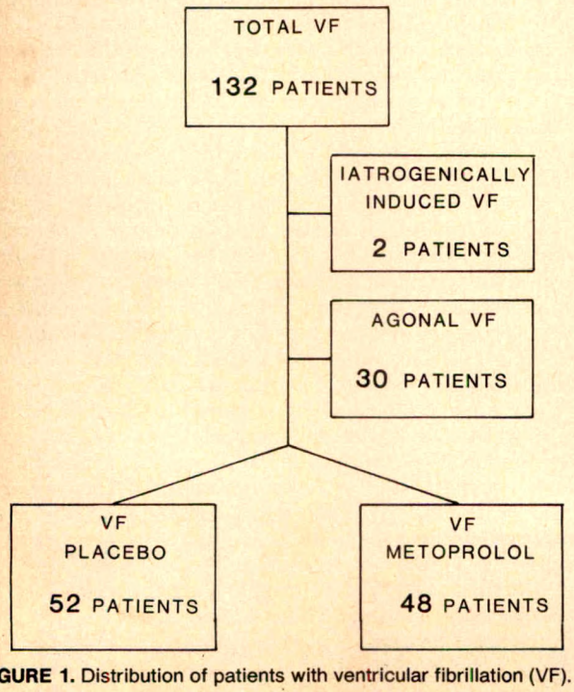

FIGURE 1. Distribution of patients with ventricular fibrillation (VF).

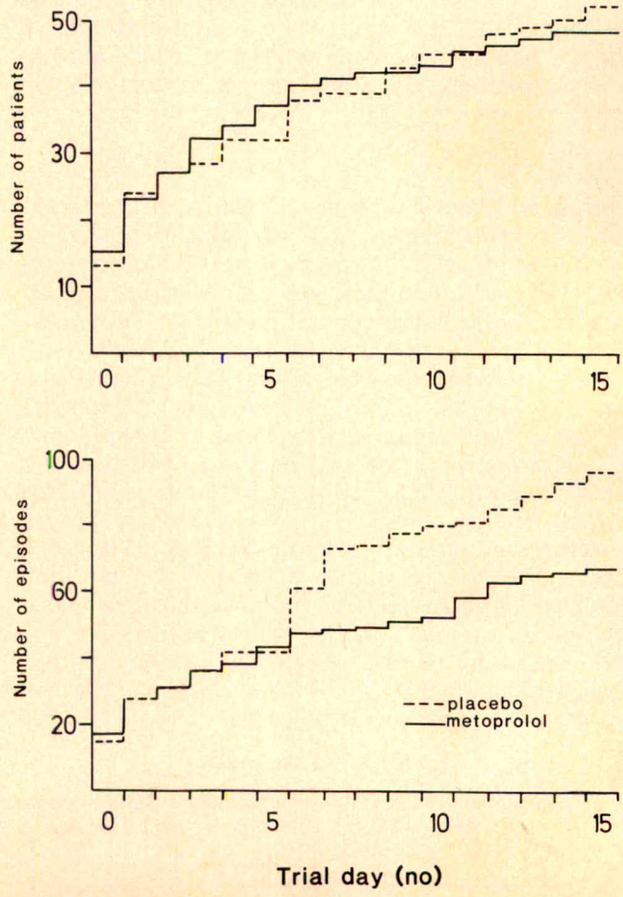

FIGURE 2. Cumulative number of patients with ventricular fibrillation (VF) and episodes of VF after randomization during the study period.

nonfatal VF was 110 in the placebo and 100 in the metoprolol group, a difference that was not significant statistically.

Supraventricular tachyarrhythmias: There was a lower number of patients with atrial fibrillation or flutter in the metoprolol group during days 0 to 15 ($p = 0.010$) and days 0 to 5 ($p = 0.017$) (Table I, Fig. 5). The reduction of other supraventricular tachycardias was also pronounced during both time periods ($p < 0.001$) (Table I, Fig. 6).

Bradyarrhythmias: Slightly more patients developed first-degree atrioventricular block in the metoprolol group during the early phase ($p = 0.028$) and there was a tendency still evident when the whole study period (days 0 to 15) was considered ($p = 0.075$). No difference was observed between the 2 groups for atrioventricular block II to III or asystole necessitating treatment (Table I).

Use of antiarrhythmic drugs: Antiarrhythmic agents were widely used, in particular during days 0 to 5, despite the recommendations in the manual of procedures. Antiarrhythmic drugs tended to be used more often in the placebo patients (19.7%) than in the metoprolol patients (17.9%) during days 0 to 5 ($p = 0.09$). The corresponding figures for days 0 to 15 were similar (Table I), and the difference for this period was significant ($p = 0.03$). There was a lower use ($p < 0.001$) of digitalis in the metoprolol patients (13.6%) compared with placebo patients (16.6%) during the whole study period and during days 0 to 5 (10.6 vs 14.2%, respectively) (Table I).

TABLE I Arrhythmic Events and Use of Antiarrhythmic Therapy During the Trial Period

Time Period (days)	Events/Use of Drugs	% Pts (no. of pts) with Event/Use of Drugs: Placebo	Metoprolol
0 to 15	VT, electrically converted	1.4 (40)	1.3 (37)
	Asystole, treated	2.2 (64)	2.6 (74)
	AV block I	2.5 (72)	3.3 (95)
	AV block II to III	5.3 (153)	5.6 (160)
	Atrial fibrillation/flutter	10.3 (298)	8.3 (238)
	Other SVT (>120 beats/min)	9.1 (265)	4.4 (125)
	Antiarrhythmics	21.5 (624)	19.2 (552)
	Cardiac glycosides	16.6 (482)	13.6 (391)
0 to 5	VT, electrically converted	1.0 (28)	1.0 (30)
	Asystole, treated	1.8 (51)	2.1 (61)
	AV block I	2.1 (62)	3.1 (89)
	AV block II to III	4.7 (137)	5.3 (153)
	Atrial fibrillation/flutter	9.2 (268)	7.5 (215)
	Other SVT (>120 beats/min)	8.2 (238)	3.9 (106)
	Antiarrhythmics	19.7 (572)	17.9 (516)
	Cardiac glycosides	14.2 (411)	10.6 (304)

AV = atrioventricular; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Discussion

The 2 groups were seemingly well balanced in terms of factors of particular importance for the arrhythmia analyses, i.e., proportion of patients with arrhythmias and treatment with antiarrhythmic agents before randomization. However, it should be noted that there were 14 patients more in the placebo group who had prerandomization VF. It was most likely that these patients entered the trial receiving lidocaine prophylaxis, and thus may have introduced some imbalance in the 2 major treatment groups at randomization.

The lack of a significant effect of metoprolol on the occurrence of VF and VT is in contrast with previous findings of a prophylactic effect of metoprolol against VF in early myocardial infarction.[2] It also contrasts a recent report on the prevention of VF during AMI by intravenous followed by oral propranolol.[3] In the Göteborg Metoprolol Trial, both the number of patients and the number of episodes of VF and the number of patients with VT were less common among metoprolol-treated patients.[4] Serious ventricular arrhythmias in AMI have also been decreased by atenolol[5] and alprenolol.[6]

There are important differences between the Göteborg Metoprolol Trial and the present investigation.

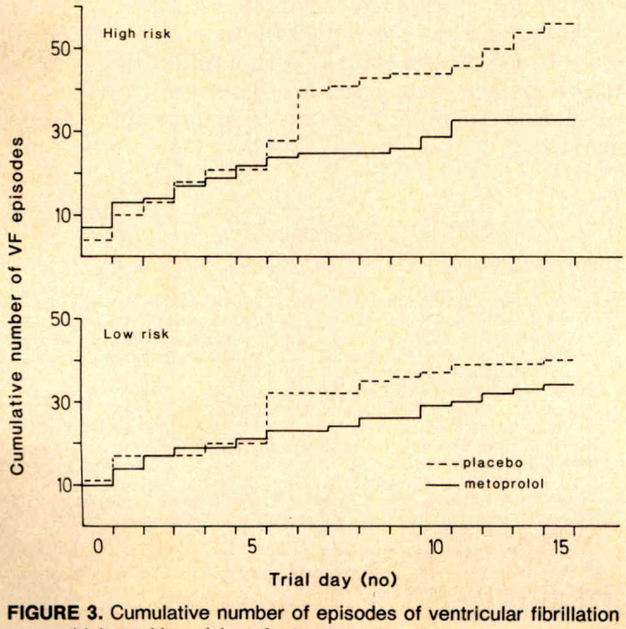

FIGURE 3. Cumulative number of episodes of ventricular fibrillation among high- and low-risk patients.

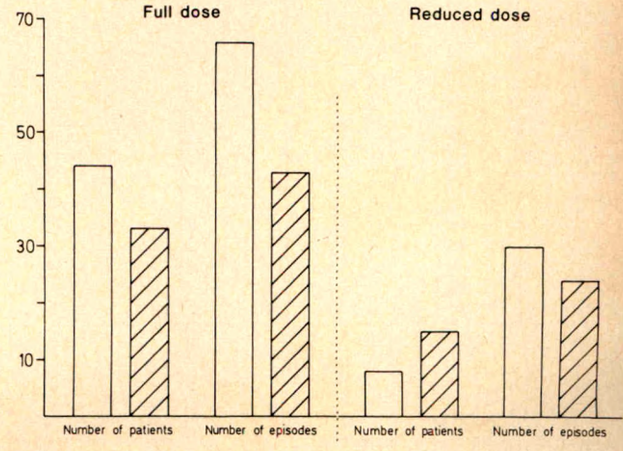

FIGURE 4. Distribution of ventricular fibrillation related to administration of trial drug.

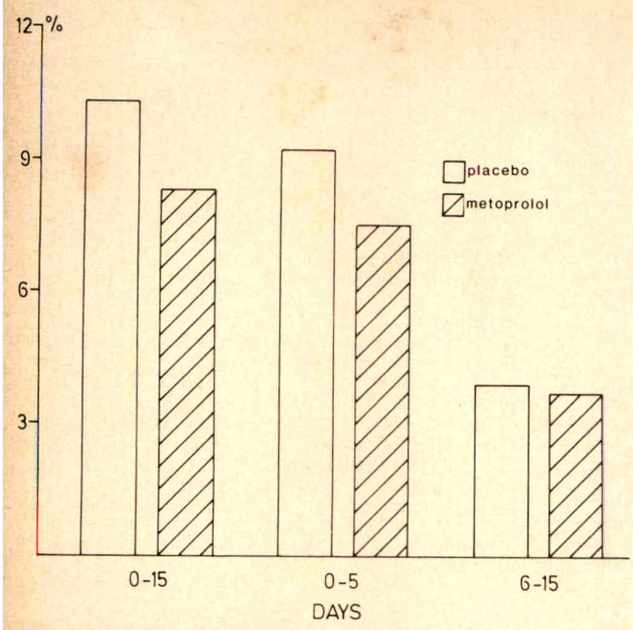

FIGURE 5. The proportion of patients with atrial fibrillation or flutter.

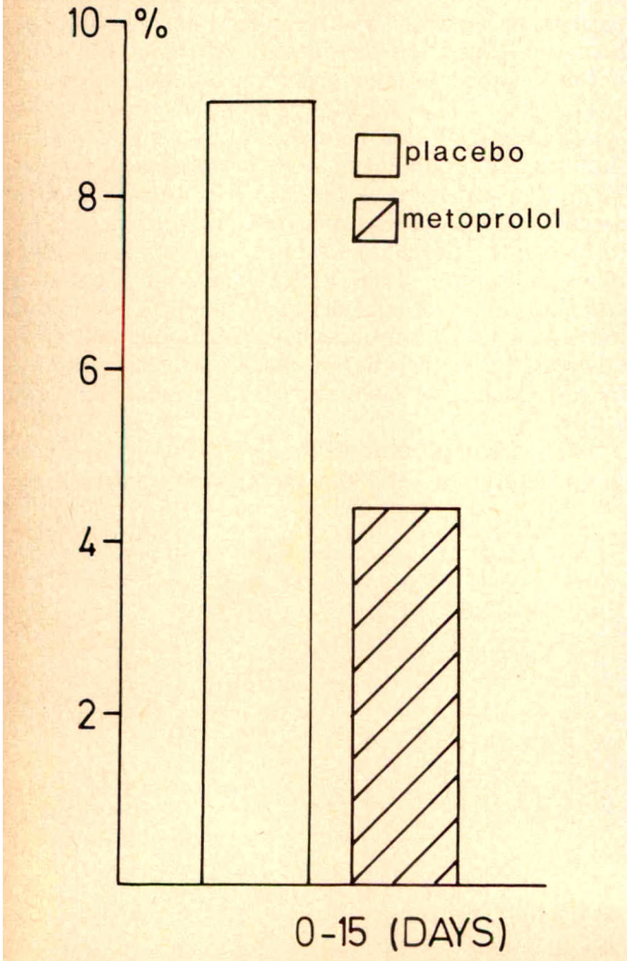

FIGURE 6. The proportion of patients with other supraventricular tachycardias (rate >120 beats/min).

The Göteborg Metoprolol Trial[2,4] included patients already on long-term β blockade. In that trial it was shown that the effect on VF was primarily on events occurring late, and the same tendency is apparent in the present trial. An effect against VF may depend more on protection against myocardial ischemia rather than on a direct electrophysiologic antifibrillatory effect. Patients already on long-term β blockade supplemented by an extra intravenous dose may become more rapidly protected than patients in whom treatment has just been started. Another reason for discrepancies between these 2 studies would be the induction of VF through discontinuation of previous β-blocking agents rather than protection through the institution of test drug. The results of the Göteborg Metoprolol Trial do not support such a conclusion, because the main reduction of VF occurred among patients not previously receiving β blockers. However, this concept is supported by another study,[3] which indicated that the protective effect of propranolol against VF within 48 hours was more pronounced in patients who had received previous β blockade. There was a remarkably high frequency (8%) of VF in those patients on previous β blockade who were randomized to the control group.

Another perhaps more important observation is the frequent use of antiarrhythmic drugs in the present trial. In the Göteborg Metoprolol Trial, lidocaine was given to only 5.5% of the placebo and 2.3% of the metoprolol patients during the complete initial hospitalization, which averaged 11 days. In the present study almost 20% of patients had received antiarrhythmic drugs during the first 5 days. It is difficult to explain the extensive use of such drugs at some hospitals without suspecting either treatment of a high number of benign ventricular arrhythmias or a prophylactic usage. The widespread usage of such drugs interferes with the possibility of testing the antifibrillatory potency of metoprolol.

A reduced incidence of supraventricular tachyarrhythmias and the use of digitalis among the metoprolol-treated patients support earlier reports.[4] The finding of no increase in asystole or important conduction disturbances supports the use of metoprolol as a safe agent.

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Other Clinical Findings and Tolerability

The MIAMI Trial Research Group

Fifteen minutes after injection there was a fall in mean heart rate (18%, p <0.001), systolic blood pressure (10%, p <0.001) and rate-pressure product (27%, p <0.0001) in the metoprolol group of patients in the MIAMI trial. Hypotension and bradycardia not necessarily associated with withdrawal of drug were more common in the metoprolol group (p <0.001). Atrioventricular block I was more common in the metoprolol group (p <0.03), whereas no such difference was observed for atrioventricular block II and III, asystole or pacemaker implantations. Left ventricular failure was observed no more often in the metoprolol group. The occurrence of cardiogenic shock also did not differ between the groups. Cardiac glycosides were used more in the placebo group, but diuretic and furosemide usage did not differ. For all patients mean furosemide doses and number of diuretic injections were similar in both treatment groups. Atropine (4.1 vs 6.4%) and sympathomimetic (3.2 vs 4.6%) agents were used more often in the metoprolol group during days 0 to 5 (p <0.05). The trial medication was withdrawn temporarily more often in the metoprolol than in the placebo group (p <0.001). However, permanent withdrawal of trial medication occurred with a similar frequency overall in both groups. More patients were withdrawn from the study because of cardiovascular reasons in the metoprolol group (9%) than in the placebo group (5%, p <0.001). Need for open treatment with a β blocker was more frequent in the placebo-treated patients (5 vs 2%, p <0.001). A multivariate analysis indicated that tolerance to metoprolol treatment was not further impaired among patients with a high-mortality risk. Early intervention with metoprolol appeared to be well tolerated generally in these patients and no subgroups could be identified in which tolerability was markedly reduced.

(Am J Cardiol 1985;56:39G–46G)

More than 10 major studies focusing on long-term β blockade after myocardial infarction have presented, in addition to mortality and morbidity data, other more general clinical findings together with data on tolerability.[1–10] Much less is known regarding the acute hospital period. The possible adverse effects of early intravenous β blockade must be considered in relation to the preexisting increased risk of severe and life-threatening complications such as heart failure, cardiogenic shock and severe arrhythmias during this early unstable stage of the disease.

In order to elucidate tolerance, safety and compliance several variables were recorded. This article will deal with patient withdrawal, adverse events, dose alterations and patient compliance. The association between permanent trial medication withdrawal and deaths on the one hand and baseline variables, mortality predictors and definite infarction diagnosis on the other will also be assessed.

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Patients and Methods

All randomized patients (n = 5,778) were included in the analysis. The clinical findings are presented for days 0 to 15 and days 0 to 5. For clarity some of the definitions of the protocol are presented below.

Hypotension: If the systolic blood pressure was ≤89 mm Hg at any time, it was recorded as hypotension.

Cardiogenic shock: For reasons of international differences of opinion regarding definition, this entity was not formally defined in the protocol. The principal investigators were asked to apply local definitions to their patients. Generally this meant that in addition to hypotension as just defined, the patients had to have oliguria or other signs of impaired peripheral circulation, e.g., pallor, clamminess or cold sweating if cardiogenic shock were to be recorded.

Drug treatment: Treatment with the following drugs was noted: cardiac glycosides,[11] diuretics, antiarrhythmics,[11] nitrates,[12] anticoagulants, atropine, sympathomimetic agents, calcium-channel blockers[12] and other vasodilators. The total dose of furosemide and the number of injections with diuretics were also recorded. Further, the number of narcotic analgesic injections was noted.[12]

Trial medication withdrawal: Predetermined guidelines for withdrawal of trial medication were presented in

TABLE I Heart Rate (HR), Systolic Blood Pressure (SBP) and Rate-Pressure Product (RPP) Before and After Injection of Placebo or Metoprolol

	Placebo (n = 2,901) Mean	SD	Metoprolol (n = 2,877) Mean	SD
Before injection				
HR	83	14	83	14
SBP	141	23	142	23
RPP × 10^{-2}	118	3	117	3
After injection				
HR	81	14	68	12
SBP	137	23	128	24
RPP × 10^{-2}	111	3	87	2

SD = standard deviation.

Table II in a previous article in this issue.[13] The trial medication could be withdrawn in 3 different ways: temporarily only, temporarily followed by permanent withdrawal and permanently only. If the treatment was temporarily withdrawn, it could be reinstituted gradually 2 days later. If the medication had to be withdrawn a second time it was then permanently withdrawn. More than 1 reason for withdrawal could be reported and thus the data were analyzed in 2 ways. The reasons for withdrawal of medication were analyzed separately. If more than 1 reason was recorded for a patient they were grouped in this consecutive order (1) cardiovascular reasons for withdrawal of trial medication, (2) need for β blockade or other reasons for treatment failure, (3) mistake, (4) unwillingness, (5) noncardiovascular adverse events and (6) others. If treatment was both temporarily and later permanently withdrawn, then only the reasons for permanent withdrawal were recorded. The time of permanent withdrawal was also recorded.

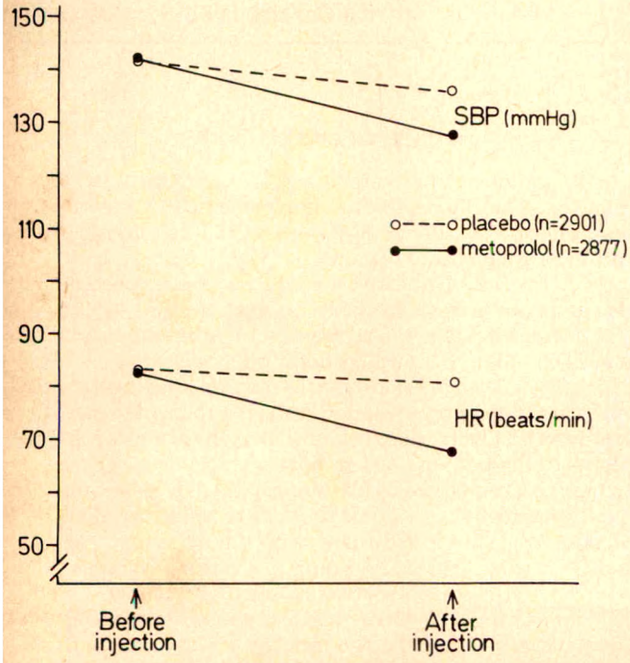

FIGURE 1. Reduction of heart rate (HR) and systolic blood pressure (SBP) in the placebo and metoprolol groups before injection and after 15 minutes.

Other adverse events: Apart from hypotension, bradycardia, heart failure and atrioventricular block, which were recorded elsewhere, other adverse events possibly related to the trial medication were recorded based on observation by the clinical staff or spontaneous reporting by the patient. The events were classified according to Adverse Reaction Terminology of the World Health Organization.[14]

Compliance: Compliance to trial treatment was judged by tablet counts. The number of returned tablets was recorded as was the number of days on which patients were given full dose, half dose, quarter dose and no dose. Compliance was estimated by expressing as a percentage the number of tablets not returned by the number that should have been taken based on the daily dosage recorded.

Hospital stay: The duration of the hospital period in each patient was calculated as the difference between the recorded dates of discharge and admission.

Emergency code breaking: The treatment code in sealed envelopes for individual patients was provided to all trial centers in the interest of patient safety. These were required to be returned at the end of the study with explanation for opened envelopes.

Statistical methods: The principles of statistical analysis previously described were generally applied.[13]

Results

Mean heart rate, systolic blood pressure and their product did not differ between the placebo and metoprolol groups before injection (Table I). In the placebo group these variables did not differ 15 minutes after injection, but in the metoprolol group they decreased ($p < 0.001$) by 18%, 10% and 27%, respectively (Fig. 1).

Mortality in the metoprolol group was not associated with reduction in heart rate, blood pressure or rate-pressure product.

Clinical observations not necessarily associated with withdrawal of trial medication are presented in Table II. Hypotension and bradycardia were more common in the metoprolol group ($p < 0.001$ and $p < 0.001$, respectively). Atrioventricular block I was more common in the metoprolol group during days 0 to 5 ($p < 0.03$); no such difference was observed for atrioventricular block II and III, asystole or pacemaker implantations. Atrial fibrillation or flutter was observed less often in the metoprolol group. Similarly, other supraventricular tachyarrhythmias were seen only half as frequently in the metoprolol patients as among placebo patients.[11] The occurrence of left ventricular failure or cardiogenic shock did not differ between the groups.

The use of concomitant medication during the whole study period (days 0 to 15) and the early phase (days 0 to 5) is presented in Table III. The data on cardiac glycosides and other antiarrhythmics have been considered in more detail elsewhere in this issue,[11] as have those for treatment of chest pain.[12] In general these agents were used less often in the metoprolol group. Other vasodilators also tended to be less used in the metoprolol group during days 0 to 5 ($p = 0.11$) and days 0 to 15 ($p = 0.09$).

The frequency of diuretic and furosemide usage did not differ between the treatment groups ($p > 0.20$), nor did the average number of diuretic injections or dose

TABLE II Other Clinical Findings

	Days 0 to 5		Days 0 to 15	
	Placebo %	Metoprolol %	Placebo %	Metoprolol %
Hypotension	8.1	16.5	9.8	18.4
Bradycardia	4.1	11.5	4.8	12.9
AV block I	2.1	3.1	2.5	3.3
AV block II	2.8	3.1	3.1	3.2
AV block III	1.9	2.3	2.1	2.4
Pacemaker implantation	1.1	1.4	1.2	1.4
Atrial fibrillation/flutter	9.2	7.5	10.3	8.3
Other SV tachyarrhythmia	8.0	3.7	9.1	4.3
Left ventricular failure	20.3	21.0	22.8	24.3
Cardiogenic shock	2.4	2.4	3.2	3.0

AV = atrioventricular; SV = supraventricular.

TABLE III Concomitant Treatment and Mortality

	Days 0 to 5		Days 0 to 15		Days 0 to 15	
	Placebo (n = 2,901) %	Metoprolol (n = 2,877) %	Placebo (n = 2,901) %	Metoprolol (n = 2,877) %	No. of Deaths (no. of treated pts.) Placebo	Metoprolol
Cardiac glycosides	14.2	10.6	16.6	13.6	47 (482)	36 (391)
Diuretics	38.5	38.8	41.6	42.9	91 (1,206)	91 (1,233)
Furosemide	32.0	33.0	34.5	36.2	. . .	. . .
Antiarrhythmics	19.7	17.9	21.5	19.2	55 (624)	50 (552)
Nitrates	48.7	46.3	55.3	53.1	60 (1,602)	55 (1,527)
Anticoagulants	60.1	60.0	61.7	61.3	94 (1,788)	74 (1,762)
Atropine	4.1	6.4	4.7	7.1	44 (135)	50 (205)
Sympathomimetics	3.3	4.6	4.2	5.7	77 (121)	69 (163)
Calcium-channel blockers	7.8	5.9	11.8	8.8	14 (343)	13 (252)
Other vasodilators	4.9	4.0	6.0	4.9	14 (174)	10 (142)

TABLE IV Diuretic and Narcotic Analgesic Treatment Among All Patients and Patients Receiving Such Treatment

	All Patients						Patients Receiving Such Treatment					
	Placebo			Metoprolol			Placebo			Metoprolol		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Days 0 to 15												
Furosemide dose (mg)	173	432	2,899	185	460	2,876	501	613	1,001	511	648	1,041
Diuretic injections	0.9	3.0	2,899	1.0	3.0	2,876	3.6	5.2	727	3.6	5.0	751
Analgesic injections	2.31	4.2	2,899	1.9	3.8	2,876	4.7	4.9	1,432	4.3	4.7	1,269
Days 0 to 5												
Furosemide dose (mg)	70	173	2,899	70	174	2,876	218	248	927	211	250	950
Diuretic injections	0.7	2.1	2,899	0.7	2.0	2,876	3.0	3.5	682	3.0	3.2	715
Analgesic injections	2.1	3.7	2,899	1.7	3.3	2,875	4.4	4.3	1,389	4.1	4.0	1,225

SD = standard deviation.

of furosemide among all patients or among those receiving such treatment (Table IV). Atropine and sympathomimetics were used more often in the metoprolol group ($p < 0.05$) but the absolute frequency was low. The relation between placebo and metoprolol regarding mortality was unassociated with the concomitant use of other drugs (Table III).

There was no difference between the treatment groups in the mean time between randomization and discharge from hospital—10.4 days (standard deviation 6.8) compared with 10.3 days (standard deviation 5.7) in the placebo and metoprolol groups, respectively.

Trial medication withdrawal: The trial medication was withdrawn temporarily more often in the metoprolol than the placebo group ($p < 0.001$). Similar findings were seen in the frequency with which medication was withdrawn first temporarily and then per-

TABLE V Proportion and Number of Patients in Whom Treatment Was Temporarily and Permanently Withdrawn

	Placebo		Metoprolol	
Temporarily only	2.9	83	6.4	185
Temporarily and permanently	0.6	16	1.8	51
Permanently only	13.3	385	13.6	390
All permanently	13.8	401	15.3	441

manently. However, the overall rate of permanent withdrawal of trial medication did not differ between the treatment groups (Table V).

The reasons for withdrawing medication temporarily only or permanently (Tables VI and VII) differed between the placebo- and metoprolol-treated groups. In both cases more patients in the metoprolol group were withdrawn from the study because of cardiovascular reasons, i.e., hypotension, heart failure and bradycardia, than in the placebo group ($p < 0.001$, Tables VI and VII). Need for open treatment with β blockade was more frequent in the placebo-treated group ($p < 0.001$). There was a tendency ($p = 0.062$) for atrioventricular block to be given more often as a reason for permanent withdrawal in the metoprolol group.

The number of patients permanently withdrawn immediately after the intravenous injection and their subsequent mortality are shown in Table VIII. There was little difference between the treatment groups in the number of deaths, despite more patients discontinuing metoprolol treatment. The number of deaths among all permanently withdrawn patients was 47 in the placebo group and 43 in the metoprolol group (Table VII). The number of deaths for separate and grouped reasons for withdrawal is presented in Table VII and indicates that metoprolol treatment was not associated with harm in any subgroup.

The cumulative number of patients permanently withdrawn by time in the placebo and metoprolol groups is presented in Figure 2. The risk of withdrawal of any kind was highest on days 0 to 2. After day 6 there were only small differences between the placebo and metoprolol groups regarding risk of withdrawal because of any reason.

Permanent withdrawal was more frequent among patients with pulmonary rales on entry, history of congestive heart failure or diuretic treatment before entry. These risk factors did not influence the relative withdrawal rate between the 2 treatment groups. When permanent withdrawals for cardiovascular reasons were analyzed according to mortality risk groupings (Table IX), the frequency of withdrawal tended to rise with the placebo group mortality but trial treatment did not appear to influence this association. The independent variables from the logit model applied to mortality[15] were used in an analysis with this method and the dependent variable was a combination of deaths and permanent withdrawals for cardiovascular reasons. This analysis showed that metoprolol was significantly associated with withdrawal for cardiovascular reasons. No other significant interactions were found. Thus there were no indications of impaired tolerance among high-risk patients.

Other adverse events: There were more patients in the metoprolol group with adverse events other than hypotension, bradycardia, congestive heart failure or atrioventricular block ($p = 0.002$) (Table X). The nature of these events is specified in Table XI.

Events commonly associated with β blockade were reported more often in the metoprolol than in the placebo group. In the metoprolol group they tended to be somewhat more pronounced and were more often associated with dose reductions compared with placebo. No serious or life-threatening events were considered to be due to the trial medication.

Dose level, compliance and emergency code breaking: A higher number of patients in the metoprolol group completed the trial after having taken reduced doses (Table XII, $p < 0.001$). The proportion of patients on each trial day who were on full dose, reduced dose, withdrawn or dead is summarized in Figure 3.

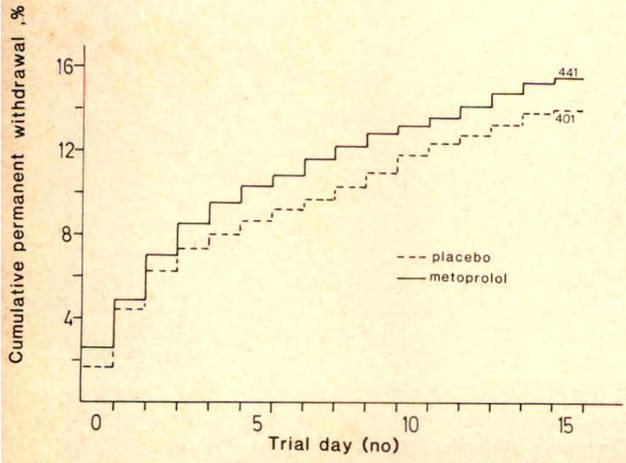

FIGURE 2. Cumulative permanent treatment withdrawals. Cumulative number of patients by trial day.

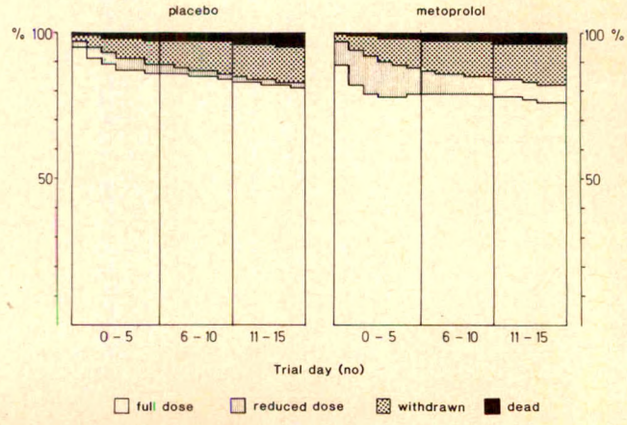

FIGURE 3. Percentage of patients by trial day divided into deaths, temporary and permanent withdrawals and reduced and full doses.

TABLE VI Number of Patients in Whom Treatment Was Temporarily or Permanently Withdrawn in Hierarchic Groups

Hierarchic Group*	Pts. Temporarily Withdrawn		Pts. Permanently Withdrawn			
			No. of withdrawals		No. of deaths	
	Placebo	Metoprolol	Placebo	Metoprolol	Placebo	Metoprolol
Cardiovascular	64	157	142	254	40	37
Need for β blockade (other treatment failure)	1	2	144	58	4	3
Mistake	8	8	32	33	0	0
Unwillingness	0	1	24	30	0	0
Adverse event	2	7	33	46	1	3
Other	8	10	26	20	2	0
Total	83	185	401	441	47	43

* Patients with more than 1 reason are placed in the highest, most appropriate group.

TABLE VII Reasons for Withdrawing Patients Temporarily or Permanently from Study Medication and Mortality

Reason*	Pts. Temporarily Withdrawn				Pts. Permanently Withdrawn			
	Placebo		Metoprolol		No. of withdrawals		No. of deaths	
	%	n	%	n	Placebo	Metoprolol	Placebo	Metoprolol
Hypotension	1.1	31	3.3	96	76	136	33	26
AV block	0.7	20	0.9	26	40	59	7	10
Heart failure	0.3	9	0.8	22	64	93	25	21
Bradycardia	0.5	15	2.0	56	34	85	10	7
Need for β blockade	0.0	1	0.0	0	144	47	6	1
Other	0.8	23	1.2	34	163	190	13	14

* More than 1 reason per patient is possible.
AV = atrioventricular.

TABLE VIII Permanent Withdrawal of All Oral Treatment After the Initial Intravenous Dose and Mortality

Initial Intravenous Dose (ml)	No. of Permanent Withdrawals		No. of Deaths	
	Placebo	Metoprolol	Placebo	Metoprolol
0	13	9	2	0
5	3	5	1	4
10	2	13	1	1
15	4	10	2	2

TABLE IX Proportion and Number of Patients in Whom Treatment Was Permanently Withdrawn for Cardiovascular Reasons by Risk Group* and Number of Deaths in These Patients

	Permanent Withdrawals				Deaths	
	Placebo		Metoprolol		Placebo	Metoprolol
	%	n	%	n	n	n
All patients	4.9	142	8.8	254	40	37
High risk	6.8	70	10.5	106	30	18
Low risk	3.8	72	7.9	148	10	19

* Risk groups are described in Table VI in the article on mortality, pages 15G–22G, this issue.

Information on returned tablets was available for 82% of patients and indicated on average that the placebo group had used 98% of their tablets and the metoprolol group 96%, which was not significantly different.

At the completion of the study, the individually sealed envelopes were returned to the Data Management Center for all randomized patients except 228. The code was broken by the clinical investigators for 128 patients in 36 of the 104 participating centers.

TABLE X Number of Patients Reporting Adverse Events (excluding hypotension, AV block, heart failure and bradycardia)

No. of Adverse Events	Placebo	Metoprolol
1	108	149
2	12	19
3	3	8
Total patients	123	176

AV = atrioventricular.

TABLE XI Number of Adverse Events

Code No*	Class of Disorder	Placebo	Metoprolol
100	Skin and appendages	16	12
410	Central and peripheral nervous system		
	Dizziness	12	15
	Headache	5	13
	Confusion	0	4
	Paresthesia	0	4
	Vertigo	0	3
	Others	0	3
431	Vision	1	2
432	Vestibular	0	1
433	Other special senses (taste)	4	0
500	Psychiatric		
	Nightmare	0	5
	Sleep disorder/somnolence	9	12
	Hallucinations	0	3
	Depression	1	4
	Others	2	5
600	Gastrointestinal		
	Nausea	8	16
	Vomiting	1	2
	Dyspepsia	4	6
	Others	12	14
700	Liver and biliary	0	2
800	Metabolic and nutrition	2	1
1010	Cardiovascular, general	2	3
1020	Myocardial	9	4
1030	Heart rate and rhythm	9	2
1040	Vascular (extra-cardiac)	9	19
1100	Respiratory system	19	18
1220	White cell and reticulo-endothelial system	0	1
1230	Platelet bleeding and clotting	0	1
1300	Urinary	0	1
1810	General disorders		
	Fatigue	11	20
	Asthenia	1	4
	Others	4	9
1830	Resistance mechanism	0	2
	Total	141	211

* WHO organ class code.

Envelopes were known to be mistakenly opened in 75 cases. Thus the code was broken in the interest of patient safety in 31 placebo-treated and 22 metoprolol-treated patients.

Discussion

It is well established that β blockade introduced both early and late markedly reduces long-term mortality after myocardial infarction. Concern about adverse hemodynamic reactions to β blockade in patients in a very early phase of myocardial infarction has contributed to limiting early administration of β blockers

TABLE XII Percentage of Patients on Full and Reduced Dose of Trial Medication for Different Time Periods

	Placebo (n = 2,901)	Metoprolol (n = 2,877)
Full oral dose	81.2	72.5
Reduced dose		
1–3 days	3.6	4.9
4–6 days	3.7	5.4
7–9 days	2.3	4.0
10–12 days	2.3	3.2
13–15 days	5.5	6.4
16 days	1.4	3.6

to patients with suspected acute myocardial infarction (AMI) in comparison with chronic treatment starting late in survivors of AMI. This apprehension has restricted early intervention mostly to patients with uncomplicated myocardial infarction. Such patients were included in the present study but so were others with mild cardiac decompensation as reflected by pulmonary rales at entry. It should be noted that the protocol of the MIAMI trial excluded patients with a heart rate $\leq$65 beats/min or systolic blood pressure $\leq$105 mm Hg.

The incidence of cardiovascular adverse events, the ensuing numbers of patients in whom treatment was permanently discontinued and the number of deaths among these treatment withdrawals provide accumulating evidence that metoprolol treatment was not harmful. The desired pharmacologic effects of this intervention are also manifested clinically by a higher incidence of bradycardia and hypotension in the metoprolol-treated patients. There was no difference from the placebo-treated patients in the overall occurrence of such undesirable situations as left ventricular failure, cardiogenic shock, asystole and high-degree atrioventricular block. The severity of the observed hypotension, bradycardia, left ventricular failure and atrioventricular block was such that treatment was permanently discontinued more often and atropine and sympathomimetics were administered more frequently in the metoprolol group. Nevertheless, the absolute number of patients who subsequently died among these withdrawals tended to be lower in the metoprolol group.

Although a higher proportion of patients in the metoprolol group deteriorated in association with the intravenous loading dose such that no further treatment was administered, the number and temporal pattern of deaths among these early withdrawals were similar for both treatment groups.

No indication was detected suggesting that withdrawal was associated with an increased mortality that was different in the 2 treatment groups. Mortality was not associated with delay time or hemodynamic response during the injection phase. The multivariate analyses disclosed an association between trial treatment with metoprolol and permanent withdrawal but no other significant interactions. This observation

supports the relevance of the exclusion criteria applied on admission to the trial.

A high proportion of the patients in the 2 treatment groups continued the entire trial period without endpoints or withdrawals on full oral dose. This supports that patient tolerance was good. As previously noted, patient compliance was high as indicated by the tablet counting results.

The pattern of reasons for withdrawal in the 2 treatment groups in this study corresponds with previous experience[5] and was unassociated with delay time. No interaction was detected between the delay time and the effect of metoprolol on incidence of left ventricular failure or of the use of diuretics during the trial period. Therefore, it has not been possible to find evidence that the timing of the institution of metoprolol treatment within the first 24 hours after the onset of symptoms has any influence on the tolerability of this regimen.

Noncardiovascular adverse events were reported more frequently for metoprolol-treated patients but did not result in an increased need to discontinue patients permanently. The spontaneous nature of the adverse event-reporting system and the seriousness of the patients' clinical conditions would tend to dampen the frequency of reporting of these noncardiovascular events. Nevertheless, some known β-blocker adverse reactions have emerged in the metoprolol-treated patients but they did not precipitate a significantly higher rate of withdrawal and were unrelated to mortality. These findings are in agreement with experiences from other large-scale postinfarction studies.[16] In most large, late-entry studies the overall proportion of adverse effects has been quite similar in the placebo and treatment groups.[4,6,8]

The combination of metoprolol and other drug treatment did not appear to worsen patient prognosis for any of the documented concomitant therapies.

Patients with evidence of congestive heart failure at entry as reflected by the presence of pulmonary rales or the use of diuretics before randomization were not adversely affected by metoprolol treatment compared with those patients without signs of heart failure at entry. Thus, mild cardiac decompensation should not be a contraindication to early intervention with metoprolol.

The central hemodynamic effects of metoprolol during the 24 hours after entry have been studied in a subset of patients in the MIAMI trial.[17] Heart rate, systolic blood pressure and cardiac index were all immediately reduced by 10 to 20% in the metoprolol group and the difference compared with placebo was maintained throughout the 24 hours. Pulmonary capillary wedge pressure (PCWP) in the metoprolol group increased only marginally 30 minutes after injection and the increase was seen only in the patient group with initial PCWP below the median of 13 mm Hg. In patients with initial PCWP above the median a continuous decrease was observed. Thus high initial PCWP was not associated with intolerance to metoprolol.

The experience from this and the previous Göteborg Metoprolol Trial concerning the development of congestive heart failure is somewhat different.[18] The previous study indicated that during the first 4 days after start of treatment there was a significant reduction in the requirement for furosemide in the metoprolol-treated patients despite no difference in the frequency of congestive heart failure between the treatment groups. In the present study there was no difference in the incidence of heart failure during the early phase but, in contrast to the previous study, there was no difference in the use of furosemide between the 2 treatment groups. It would seem, however, that the use of furosemide is poorly related to the recorded variable of left ventricular failure in the present study, because 33% of patients received furosemide during days 0 to 5 while only 21% were reported to have congestive heart failure.

The Belfast Metoprolol Trial[19] found no evidence that metoprolol treatment in patients with AMI significantly increased the risk of heart failure. Similarly, studies of early intravenous treatment with atenolol,[20] propranolol[21] and timolol[22] in patients with suspected AMI have detected no association between β-blocker treatment and the development of heart failure or atrioventricular block.

It appears that early intervention with metoprolol has been generally well tolerated in these patients and no subgroups could be identified in which tolerability to metoprolol was markedly reduced.

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Hemodynamic Effects of Metoprolol in Acute Myocardial Infarction*

A Randomized, Placebo-Controlled Multicenter Study

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The central hemodynamic effects of metoprolol in acute myocardial infarction have been studied in a multicenter, double-blind, randomized trial. One hundred and ninety patients with acute myocardial infarction not previously on β blockers with heart rate >65 beats/min and blood pressure >105 mm Hg and without clinical signs of serious heart failure were included. After insertion of a pulmonary artery catheter, patients were randomized to metoprolol, 15 mg intravenously, and 50 mg 4 times a day orally (n = 95) or placebo (n = 95) with a mean delay of 7.2 hours. Hemodynamic measurements were made at baseline and repeatedly during 24 hours. Heart rate, systolic blood pressure and cardiac index were all immediately reduced by 10 to 20% in the metoprolol group and the difference compared with placebo was maintained throughout the 24 hours ($p < 0.001$). Pulmonary capillary wedge pressure (PCWP) in the metoprolol group increased from 13.7 ± 6.7 to a peak of 15.5 ± 5.5 mm Hg 30 minutes after injection. The difference compared with placebo was maintained for 8 hours ($p < 0.01$). This increase was seen only in the patient group with initial PCWP below the median of 13 mm Hg. In patients with initial PCWP above the median a continuous decrease was observed in both the placebo and metoprolol groups. Thus high initial PCWP was not associated with intolerance to metoprolol. Based on hemodynamic measurements tolerance to metoprolol was good.

(Am J Cardiol 1985;56:47G–54G)

Previous reports concerning the hemodynamic effects of acute β blockade in patients with acute myocardial infarction (AMI) have been based on small numbers of patients given the drugs openly and without control groups.[1–9] In the early phase of AMI it is difficult to predict from a clinical examination the corresponding central hemodynamics.[10,11] Further, there might be a time lag between hemodynamic changes and clinical findings.[12] The central hemodynamic response to β blockade in this setting is, therefore, incompletely understood.

The metoprolol in acute myocardial infarction (MIAMI) trial[13] was a large, randomized, double-blind, placebo-controlled, multicenter study. The primary objective of the trial was to study the effect of metoprolol on 15-day mortality. It also provided a unique opportunity to investigate the early hemodynamic response to metoprolol.

The purpose of the present study was to analyze the central hemodynamic changes during the first 24 hours after intravenous and oral administration of metoprolol in patients with a definite myocardial infarction.

Methods and Patients

Patients with suspected myocardial infarction admitted to participating coronary care units were eligible for the

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* This manuscript was reviewed and accepted for publication in the regular issues of the AJC, but the authors elected to have it published with the other MIAMI supplement articles.

TABLE I Participating Centers, Number of Patients and Physicians Responsible for the Hemodynamic Optional Study

Center	No. of Patients	Responsible Physician
Canada		
Royal Alexandra Hospital, Edmonton	6	W. P. Klinke
The Netherlands		
Academisch Ziekenhuis Groningen, Groningen	17	P. Dunselman
Algemeen Ziekenhuis Zonnestraal, Hilversum	2	K. L. Liem
St. Ignatius Ziekenhuis, Breda	34	H. M. A. Corbeij L. G. P. M. van Zeijl
St. Oosterschelde Ziekenhuizen, Goes	7	H. W. O. Roeters Van Lennep A. Liem
Thoraxcentrum, Rotterdam	1	M. Simoons
Sweden		
Central Hospital, Skövde	6	L. Rydén, P. Smedgård
Sahlgrenska Hospital, Göteborg	13	A. Hjalmarson, S. Holmberg F. Waagstein
Söder Hospital, Stockholm	1	J. Hulting
Varberg Hospital, Varberg	6	J-E. Olaison, L. Waagstein
Östra Hospital, Göteborg	38	P. Held, K. Swedberg, A. Vedin
United Kingdom		
East Birmingham Hospital, Birmingham	54	W. Littler, D. Murray
Selly Oak Hospital, Birmingham	1	R. E. Nagle
West Germany		
Städt. Kliniken, Dortmund	4	D. Klaus
Total	190	

study. Fourteen of the 104 MIAMI centers participated in this optional study (Table I).

The inclusion criteria were: (1) age <75 years, (2) onset of chest pain within 12 hours of catheterization; patients admitted between 12 and 24 hours from onset of symptoms were eligible if heart rate was >90 beats/min, if pulmonary rales were present <10 cm above the lower border or if there was persistent or recurrent chest pain and (3) electrocardiographic signs of AMI with ST elevation or new Q waves.

The exclusion criteria were as follows: (1) current treatment with β-adrenergic blockers or calcium-channel blockers, (2) heart rate ≤65 beats/min, (3) systolic blood pressure ≤105 mm Hg, (4) clinical signs of left ventricular failure, as defined by basal pulmonary rales on auscultation >10 cm, (5) P-Q interval >0.24 seconds or higher degree of atrioventricular block, (6) severe chronic obstructive pulmonary disease or other serious disease with impact on short-term prognosis, (7) implanted pacemaker or (8) resuscitation outside hospital.

Of the 5,778 patients enrolled in the MIAMI trial, hemodynamic data from 201 were received at the Data Management Center. However, data from 11 of these patients were excluded from further analysis because of violations of the entry criteria. Of these, 9 patients did not have electrocardiographic signs of AMI at randomization and did not develop AMI. One patient was withdrawn before blind drug injection and another patient did not receive the blind drug until after 4 hours.

The remaining 190 patients fulfilled the protocol criteria and were randomized according to the MIAMI protocol. There was no separate stratified randomization of these patients; however, the goal was at least 150 patients and this number was considered likely to give a balanced randomization. Informed consent was obtained. Protocol was approved by the Ethical Committee at each participating center.

Clinical management and study variables: All patients underwent right-sided heart catheterization at bedside with a triple lumen balloon-tipped thermistor catheter.[14] Pressures were recorded by means of strain gauge transducers. The reference level was 5 cm below the sternum in the supine position. Cardiac output was determined with the thermodilution method; each recorded value was based on a mean of at least 2 accepted measurements within 10%. All measurements and pressure curves were recorded on paper and saved for later analyses.

An arterial catheter was positioned in the radial, brachial or femoral artery (East Birmingham Hospital used cuff readings only). After insertion of the catheters the patients rested 10 minutes; then a control reading including cardiac output, arterial pressures, heart rate, mean right atrial pressure, pulmonary artery pressure and mean pulmonary capillary wedge pressure (PCWP) was performed. The study drug (metoprolol, 15 mg, or placebo) was then administered intravenously in 3 divided doses with 2-minute intervals, according to the MIAMI protocol. Oral drug (metoprolol, 50 mg, or placebo) was given immediately after the 10-minute and 6-, 12- and 18-hour readings. If necessary, dose adjustments were made according to the MIAMI protocol. Hemodynamic measurements were repeated at 10 and 30 minutes, as well as after 1, 2, 4, 6, 8, 12, 18 and 24 hours.

The following indexes were derived from the measurements obtained. Left ventricular stroke work index equalled (mean systolic arterial pressure − PCWP) × stroke volume index × 0.0136. Systemic vascular resistance equalled 80 (mean arterial pressure − right atrial pressure)/cardiac output. Rate-pressure product equalled systolic arterial pressure × heart rate.

Medication other than the trial drug was avoided shortly before and within 30 minutes after the control readings. Administration of such drugs was intended to be based purely on bedside clinical evaluation of the patient, in a fashion identical to that of all other MIAMI patients.

Statistical analysis: At baseline a comparison of background variables was made both between the placebo and the metoprolol group, and between the hemodynamically studied patients and all MIAMI patients admitted within 12 hours with electrocardiographic signs of AMI. Chi-square tests were used for these comparisons.

TABLE II Patient Characteristics (All Randomized Patients in the MIAMI Trial, with Electrocardiographic [ECG] Signs of Infarction at Entry and Entered Within 12 Hours Are Also Compared with the Hemodynamically Studied Patients)

Characteristics	Hemodynamic Study: Placebo (n = 95) %	Hemodynamic Study: Metoprolol (n = 95) %	All MIAMI Patients with ECG Changes (n = 2,860) %
Age (years)	59±9	59±9	59±10
Men	82	82	79
Women	18	18	21
Total delay (hours)	7.3±4.1	7.2±3.6	5.6±2.8***
In-hospital delay (hours)	3.1±1.7	3.4±2.5	2.4±2.2***
Clinical history			
Previous infarction	5	5	13**
Angina pectoris	22	18	26
Congestive heart failure	2	0	3
Bypass surgery	0	0	1
Hypertension	13	7	14
Diabetes	4	4	7
Smoker	57	55	55
Chronic medication			
Digitalis	3	1	4
Diuretics	5	6	13**
Antihypertensives	5	1	5
Clinical findings			
Pulmonary rales	33	33	17***
Atrial fibrillation	1	4	3
Ventricular fibrillation	8	4	2**
Medication after admission before randomization			
Diuretics	13	15	11
Digitalis	1	3	2
Atropine	4	5	2*
Final infarct site			
Anterior	42	53	44
Inferior	44	37	37
Other	14	10	8

* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$ (hemodynamic group vs MIAMI patients). Differences between the placebo and the metoprolol groups were not significant.

Hemodynamic variables were compared at baseline and during 24 hours. At baseline this was done by means of a Student *t* test. Thereafter the variables were compared by application of the "area-under-the-curve" method. For each patient the area was calculated using the trapezoidal rule. The period 0 to 24 hours was divided into 3 intervals: 0 to 1, 1 to 8 and 8 to 24 hours. For each interval the individual area under the curve was calculated. The differences between the distributions of the areas under the curve for the whole trial period and for each interval were then tested between the placebo and metoprolol groups using a *t* test.

A p value of <0.05 was considered significant. In the text and tables, mean values ± standard deviation are presented. In figures the mean ± standard error of the mean is shown.

Data management: The same procedures as for the main MIAMI trial were used in this optional study. A 1-page report form was used and data were edited, checked and entered into the computer at the Data Management Center.[13]

Results

One hundred and ninety patients were included in the analysis. All fulfilled the criteria for a definite infarction. There were 95 patients allocated to placebo and metoprolol, respectively. At randomization, background variables were not significantly different between the 2 treatment groups (Table II). The patients in the hemodynamic protocol were also compared with all MIAMI patients who had electrocardiographic signs of AMI at entry and were randomized within 12 hours after onset of symptoms (n = 2,860). The catheterized patients compared with the other MIAMI patients had a longer delay time from onset of symptoms (7.2 ± 3.8 vs 5.6 ± 2.8 hours, $p < 0.001$). Twenty patients (11%) were randomized between 12 and 24 hours from onset of symptoms. There were fewer patients with previous myocardial infarction (5 vs 13%, $p < 0.01$) and basal pulmonary rales were twice as common (32 vs 16%, $p < 0.001$) among the catheterized patients.

Trial drug administration: Full intravenous loading dose of trial drug (15 ml) was given to all placebo patients and to 86 (91%) patients in the metoprolol group. Six of the 9 patients with reduced intravenous dose later received oral blind drug according to the MIAMI protocol. All 9 were included in the metoprolol group in the analysis.

There were 7 placebo and 8 metoprolol patients who did not receive 1 or more oral dose. This was due to hypotension in 12 patients (6 placebo, 6 metoprolol), heart failure in 2 patients (1 placebo, 1 metoprolol) and bradycardia in 1 metoprolol-treated patient.

Concomitant therapy: After randomization a total of 41 placebo- and 40 metoprolol-treated patients received some medication (including analgesics) in addi-

TABLE III Hemodynamic Observations During 24 Hours

Variable	Control		10 Minutes		30 Minutes		1 Hour		2 Hours	
	P	M	P	M	P	M	P	M	P	M
HR (beats /min)	83±13	84±14	81±15	68±12	81±14	70±11	82±16	71±12	81±14	71±12
RAP (mm Hg)	5.1±3.6	5.6±4.4	5.2±3.9	7.5±4.2	5.3±3.9	7.8±4.4	5.0±3.7	7.2±4.3	4.6±3.5	6.5±3.6
PAP (mm Hg)										
Systolic	31±10	33±11	32±10	33±9	32±12	33±9	32±10	34±9	30±9	33±9
Diastolic	14±5	15±6	14±5	15±5	15±6	15±5	14±6	15±6	13±6	14±6
Mean	21±7	22±8	22±7	22±6	21±8	22±6	21±6	23±6	20±6	22±7
PCWP (mm Hg)	13.6 ±5.8	13.7 ±6.7	13.4 ±6.1	14.8 ±5.7	13.2 ±6.5	15.4 ±5.4	12.5 ±5.6	14.7 ±5.7	11.8 ±5.5	14.1 ±5.8
SAP (mm Hg)										
Systolic	145±27	145±28	144±28	128±28	142±27	128±27	143±25	129±27	137±24	128±27
Diastolic	81±14	81±14	80±14	76±16	80±13	76±16	79±14	76±14	76±13	74±16
Mean	104±17	103±17	102±19	94±19	101±17	94±17	101±16	94±18	97±16	93±19
CO (liter /min)	5.9±1.7	5.6±1.5	5.8±1.7	4.3±1.2	5.6±1.6	4.3±1.1	5.7±1.7	4.3±1.2	5.6±1.6	4.5±1.3
CI (liter /min/m^2)	3.1±0.8	2.9±0.7	3.1±0.8	2.2±0.6	3.0±0.7	2.2±0.6	3.0±0.8	2.2±0.6	2.9±0.7	2.3±0.6
SV (ml/beat)	72±21	68±20	73±22	63±18	71±20	62±17	71±21	61±17	71±21	64±18
SVI (ml/beat /m^2)	39±10	36±10	39±11	33±9	38±9	32±8	38±9	32±9	37±10	33±9
SWI (g·m/m^2)	59±22	54±18	59±21	44±16	57±20	43±16	57±20	43±16	54±20	44±16
SVR (dynes s cm^{-5})	1,430 ±460	1,490 ±480	1,440 ±470	1,740 ±520	1,450 ±420	1,710 ±500	1,440 ±420	1,710 ±530	1,410 ±440	1,630 ±550
RPP · 10^{-2} (beats·mm Hg)	120±28	122±35	117±31	88±29	115±28	90±26	116±28	92±27	111±27	90±28

CI = cardiac index; CO = cardiac output; HR = heart rate; M = metoprolol; P = placebo; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RPP = rate-pressure product; SAP = systemic arterial pressure; SV = stroke volume; SVI = stroke volume index; SVR = systemic vascular resistance; SWI = stroke work index.

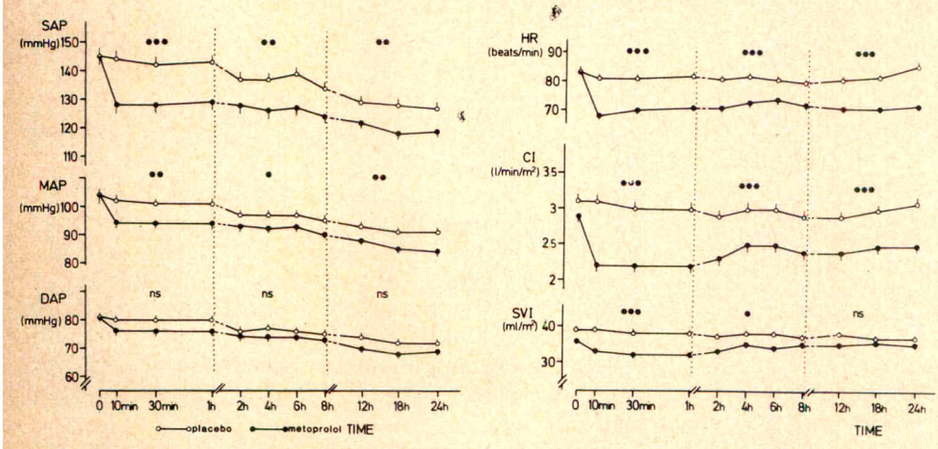

FIGURE 1. Hemodynamic profiles during the 24-hour study period. The horizontal time axis is divided into 3 periods: 0 to 1 hour, 1 to 8 hours and 8 to 24 hours. Within each period the placebo and the metoprolol groups have been statistically compared. CI = cardiac index; DAP = diastolic arterial pressure; HR = heart rate; MAP = mean arterial pressure; ns = difference not significant; SAP = systolic arterial pressure; SVI = stroke volume index. * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

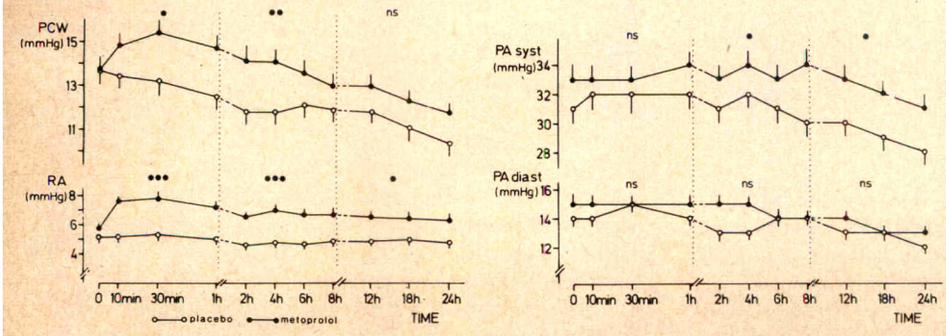

FIGURE 2. Hemodynamic profiles during the 24-hour study period. Time axis and p values as in Figure 1. PCW = pulmonary capillary wedge pressure; RA = right atrial pressure; PA syst = pulmonary artery systolic pressure; PA diast = pulmonary artery diastolic pressure.

TABLE III (cont'd.)

4 Hours		6 Hours		8 Hours		12 Hours		18 Hours		24 Hours	
P	M	P	M	P	M	P	M	P	M	P	M
82±15	73±13	81±15	74±14	80±15	72±14	81±16	71±11	82±16	71±12	86±17	72±12
4.8±3.8	7.0±3.9	4.7±4.0	6.7±3.8	4.9±3.9	6.7±4.5	4.9±3.7	6.5±4.4	5.0±4.3	6.4±4.6	4.8±4.2	6.3±4.5
31±10	34±10	31±10	33±10	30±10	34±11	30±9	33±10	29±9	32±9	28±9	31±9
13±5	15±5	14±5	14±5	14±5	14±5	13±5	14±5	13±6	13±5	12±5	13±4
20±6	22±6	20±7	22±6	20±7	21±7	19±6	21±6	19±7	20±5	18±6	20±5
11.8 ±5.5	14.1 ±5.6	12.1 ±5.8	13.6 ±5.7	11.9 ±5.5	13.0 ±5.3	11.8 ±5.1	13.0 ±5.0	11.1 ±5.3	12.3 ±4.8	10.4 ±5.2	11.8 ±4.0
137±25	126±26	139±24	127±22	134±26	124±20	129±25	122±22	128±23	118±19	127±23	119±19
77±14	74±14	76±14	74±14	75±15	73±12	74±14	70±13	72±14	68±13	72±13	69±12
97±17	92±16	97±16	93±16	95±18	90±14	93±16	88±15	91±15	85±14	91±14	84±14
5.6±1.4	4.7±1.3	5.6±1.4	4.8±1.3	5.4±1.3	4.6±1.3	5.5±1.3	4.7±1.1	5.6±1.3	4.8±1.3	5.8±1.5	4.8±1.2
3.0±0.6	2.5±0.6	3.0±0.6	2.5±0.6	2.9±0.6	2.4±0.6	2.9±0.6	2.4±0.6	3.0±0.6	2.5±0.6	3.1±0.6	2.5±0.5
71±19	67±20	71±21	67±19	70±21	66±20	71±21	67±17	70±21	69±19	69±20	68±17
38±9	35±10	38±10	34±9	37±10	35±9	38±10	35±8	37±10	36±9	37±9	35±8
55±19	46±17	55±21	46±16	53±20	45±16	51±18	45±15	52±19	45±14	50±17	45±15
1,380 ±370	1,530 ±510	1,370 ±330	1,530 ±520	1,390 ±390	1,550 ±510	1,330 ±360	1,440 ±380	1,310 ±330	1,380 ±380	1,250 ±330	1,350 ±350
112±29	92±27	113±31	94±25	107±30	90±24	105±32	87±23	105±30	84±21	110±31	85±18

tion to the trial drug. Diuretics (18 placebo, 22 metoprolol), sympathomimetics (3 placebo, 1 metoprolol) and vasodilators (7 placebo, 7 metoprolol) were equally distributed between the 2 groups.

During the first hour after randomization 6 placebo and 4 metoprolol patients received diuretics or nitroprusside or sympathomimetics.

Hemodynamic response: In Table III the overall hemodynamic findings are presented. The baseline recordings did not show any significant difference between the treatment groups in any of the variables.

Heart rate (Fig. 1) in the metoprolol group decreased from 84 ± 14 to 68 ± 13 beats/min after 10 minutes. In all the following readings heart rate continued to be significantly lower by 10 to 15% in the metoprolol compared with the placebo group ($p < 0.001$).

Systolic arterial blood pressure (Fig. 1) decreased in the metoprolol group from 145 ± 28 to 128 ± 29 mm Hg after 10 minutes. The systolic pressure continued to be lower by 5 to 10% during the observation period ($p < 0.01$). However, the diastolic pressure (Fig. 1) was not significantly lower than in the placebo group. The mean arterial pressure (Fig. 1) was reduced after 10 minutes and thereafter ($p < 0.01$).

Cardiac index (Fig. 1) was immediately reduced from 2.9 ± 0.7 to 2.2 ± 0.6 liters/min · m^2 in the metoprolol group. Thereafter a gradual increase to 2.5 ± 0.6 liters/min · m^2 after 4 hours was seen, but the difference between the treatment groups remained during the entire study period ($p < 0.001$). Reduction of cardiac index in the metoprolol patients was the same percentage in patients with an initial reading above or below the median (2.9 liters/min/m^2) −28% and 21%, respectively.

In the metoprolol group stroke volume index was reduced within the first 8 hours (Fig. 1). It fell from 36 ± 10 to 32 ± 9 ml/beat/m^2 ($p < 0.001$) after 1 hour. Thereafter a gradual increase was observed and after 8 hours no difference was observed.

The pulmonary capillary wedge pressure (PCWP) (Fig. 2) in the metoprolol group increased slightly from 13.7 ± 6.7 to a maximum of 15.3 ± 5.4 mm Hg after 30 minutes. The difference compared with the placebo group was maintained for 8 hours ($p < 0.01$). Thereafter there was no significant difference between the groups.

In the metoprolol-treated patients with an initial PCWP below the median (13 mm Hg) the pressure increased from 8.7 ± 3.5 to 12.4 ± 3.9 mm Hg after 1 hour (Fig. 3). As a result PCWP was significantly higher among metoprolol-than placebo-treated patients, with an initial reading below the median for the first 8 hours ($p < 0.05$). Above the median, the PCWP fell in the metoprolol groups from 19.4 ± 4.6 to 17.6 ± 5.7 mm Hg and in the placebo group from 18.5 ± 4.2 to 15.3 ± 5.5 mm Hg after 1 hour. For the whole observation period therefore, there was no significant difference compared with the placebo group. This dependency on initial PCWP is shown in Figure 4. It also shows the

situation for individual patients at the time for maximal change.

The patients in the upper PCWP quartile (>18 mm Hg, n = 42) were compared in the same way. The metoprolol group (n = 25) decreased from 22.1 ± 4.2 to 13.5 ± 3.6 mm Hg at 24 hours, which was not significantly different from the placebo group. Similarly, the 14 metoprolol and 11 placebo patients in the upper quartile who did not receive any medication except for the trial drug showed a pronounced decrease in PCWP. In metoprolol patients it decreased from 22.6 ± 5.1 to 13.9 ± 3.6 mm Hg and in placebo patients from 23.1 ± 3.9 to 13.6 ± 5.5 mm Hg at 24 hours.

In the metoprolol group the pulmonary artery pressures were slightly higher than in the placebo group during the observation period, but no clear differences were seen (Fig. 2). Right atrial pressure (Fig. 2) in the metoprolol group increased from 5.6 ± 4.4 to a maximum of 7.8 ± 4.4 mm Hg at 30 minutes. The difference to the placebo group was significant during 24 hours ($p < 0.01$).

Rate-pressure product (Fig. 5) fell immediately in the metoprolol group after injection and was considerably reduced throughout the study period ($p < 0.01$).

The systemic vascular resistance (Fig. 5) increased in the metoprolol group from 1,490 ± 490 to 1,730 ± 520 dynes s cm^{-5} after 10 minutes. This initial increase compared with the placebo group was maintained during the first 8 hours ($p < 0.01$); then a gradual attenuation of the difference was seen and after 8 hours no significant difference remained.

Left ventricular stroke work index (Fig. 5) was reduced from 54 ± 18 to 44 ± 16 g · m/m^2 after 10 minutes. This reduction compared with the placebo group was then maintained during the trial period ($p < 0.01$).

The metoprolol response was not associated with age, sex or delay time between onset of symptoms and randomization.

In a subgroup (n = 27, 10 placebo and 17 metoprolol patients) with initial heart rate above the median (80 beats/min), PCWP above the median (13 mm Hg) and cardiac index below the median (2.9 liters/min · m^2), the hemodynamic response to metoprolol was similar to that described for each variable. Of these patients 3 of 10 in the placebo and 2 of 17 in the metoprolol group died during the 15-day MIAMI trial period.

Of the 190 patients studied there were 9 deaths (4.7%) during the 15-day follow-up, 5 in the placebo and 4 in the metoprolol group.

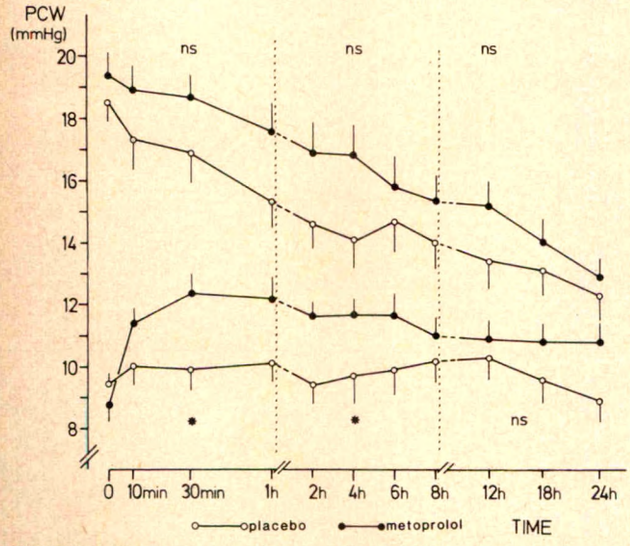

FIGURE 3. Pulmonary capillary wedge (PCW) pressure during 24 hours divided by median pressure at baseline (13 mm Hg). * = $p < 0.05$.

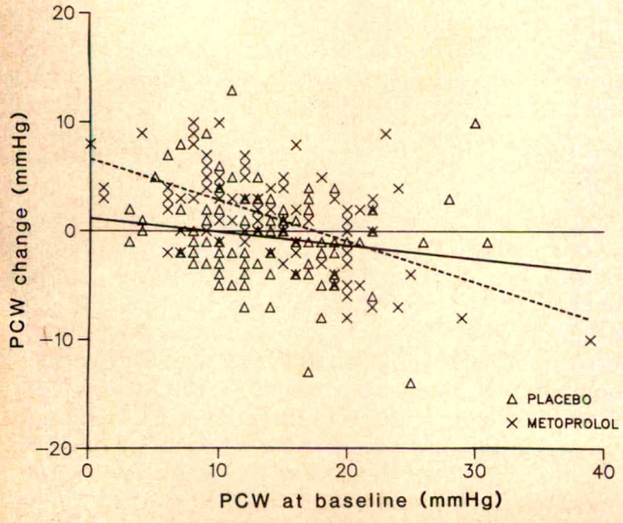

FIGURE 4. Change in pulmonary capillary wedge (PCW) pressure 30 minutes after randomization compared with PCW pressure at control. Dotted line = regression line for the placebo patients; r = −0.17; p = not significant. Solid line = regression line for the metoprolol patients; r = −0.57; $p < 0.001$.

Discussion

This study is the first large placebo-controlled evaluation of central hemodynamic effects of β blockade in AMI. The studied patients were representative of the MIAMI population with electrocardiographic signs of infarction at admission with the exception of pulmonary rales, which were more common in the first group. It is unclear if this is due to a selection of patients with higher left ventricular filling pressures or a more detailed evaluation of those patients considered for catheterization. A minor part of the difference is explained by the fact that rales were an inclusion criterion after 12 hours delay. The other differences compared with the main MIAMI population with electrocardiographic changes are the lower incidence of previous infarction and the longer delay time due to the catheterization procedure.

A number of uncontrolled studies of central hemodynamic effects of β blockade have been published.[1–9] Propranolol was studied in 7,[1–7] metoprolol[8] and practolol[9] in 1 study each. A comparison of those and the present results is difficult due to differences in patient selection and delay times. Most of these earlier data were obtained at 1 single measurement shortly after administration of the drug. In the present trial the initial reaction to metoprolol was studied as well as the hemodynamic changes during 24 hours.

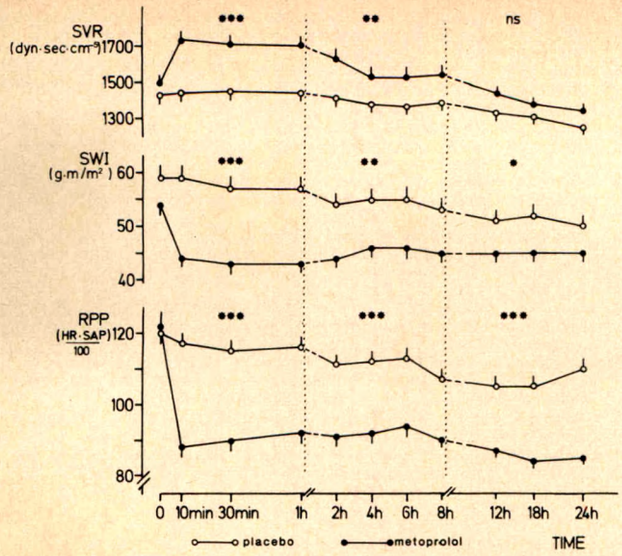

FIGURE 5. Hemodynamic profiles during the 24 hour study period. Time axis and p values as in Figure 1. SVR = systemic vascular resistance; SWI = stroke work index; RPP = rate-pressure product.

Systolic blood pressure, heart rate and thus rate-pressure product were reduced. Together with the reduction in stroke work index, this suggests a decreased myocardial oxygen consumption.[15,16] However, the diastolic arterial pressure did not fall, suggesting an unchanged myocardial diastolic perfusion pressure.

The increase in PCWP observed in the metoprolol group was small but significant compared with placebo for 8 hours. This observation of a slight increase in PCWP is in agreement with Cairns et al.[7] However, Mueller et al[4] did not find any change in PCWP in their pooled population of 55 patients treated with propranolol. The increase in PCWP in our patients was only observed in the group of patients with an initial PCWP below median.

The patients with elevated baseline PCWP are of particular interest. This patient population constitutes a high-risk group[10,11,17] with increased mortality. It is in this group that the negative inotropic effect of metoprolol is most worrisome.

However, we found a continuous decrease of PCWP in these patients. The largest decrease in PCWP was observed in the upper quartile (PCWP >18 mm Hg). There was no difference between the placebo and metoprolol groups. This decrease was found both in patients given diuretics or other drugs and in those who had no medication during the observation period. A similar observation regarding high filling pressures has been reported by Mueller et al[3] for 6 patients with initial PCWP >15 mm Hg treated with propranolol. Málek et al[8] reported a normalization of increased filling pressures in a small patient population with the same dose of metoprolol as in this study.

The decrease in PCWP among these potentially high-risk patients was similar in the placebo and metoprolol groups. It may be that in this group the negative inotropic effects of metoprolol are balanced by a more pronounced antiischemic effect on the severely hypoxic myocardium.

An alternative explanation could be "regression to the mean." However, this could not explain the different response between the placebo and metoprolol groups below and above the median PCWP.

The decrease in patients with high baseline PCWP might indicate improvement of the diastolic myocardial function owing to increased myocardial distensibility. There are several studies suggesting that the elevated PCWP in the ischemic myocardium is in fact due to increased myocardial stiffness.[18,19] However, the exact mechanism is debated.[20]

The reduction in cardiac index in the metoprolol group was mainly due to a reduction of heart rate even though a reduction of stroke volume was also observed. After 8 hours it was due entirely to the reduced heart rate. The decrease in stroke volume in metoprolol-treated patients was accompanied by an increase in PCWP. This suggests a depressed Starling curve in these patients. The importance of this observation is difficult to evaluate as an increase in filling pressure was observed only in the patient group with initial pressures below median.

The increase in systemic vascular resistance during the first 8 hours might be due to a baroreceptor-mediated direct effect on the α_1 receptors, in response to the fall in arterial blood pressure.[21] However, the circulating catecholamines could have some contributory effect on this change in vascular resistance. The hemodynamic response was not significantly influenced by age, delay time or sex. This has previously not been reported after administration of β blockers.

In summary, we have been able to describe the central hemodynamic reaction to metoprolol in patients with AMI. An acute reduction of systolic blood pressure, cardiac index and heart rate was the most impressive and consistent effect. These effects might all indicate decreased myocardial energy production and thus a reduction of myocardial oxygen consumption. An increase in PCWP was only seen in the group of patients in whom initial filling pressures were low; in contrast, the PCWP in the group with high initial values decreased in both metoprolol- and placebo-treated patients. Thus metoprolol appeared to decrease myocardial oxygen consumption without adversely affecting PCWP. With this patient selection we could not identify any subgroup of patients in which the effects of metoprolol were unfavorable.

Thus, a fall in cardiac index or blood pressure within the limits reported here should not contraindicate continued treatment, nor should high PCWP per se be an argument against metoprolol treatment. Instead, bedside clinical findings, such as systolic blood pressure and lung rales, should be evaluated when the decision to use metoprolol is made.

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General Discussion

The MIAMI Trial Research Group

The purpose of this article is to relate the results of the MIAMI trial to the findings from other postinfarction studies with β blockers and to draw general conclusions from this collective experience.

The benefit of long-term β blockade as prophylactic treatment to reduce mortality and morbidity after an acute myocardial infarction (AMI) has been unequivocally established and this therapeutic approach has gained increasing acceptance. The mortality reduction amounts to about 25% after 3 years of follow-up in well-conducted trials.[1,2] These results have been obtained mainly in studies in which the oral treatment has been started at least 5 days after confirmation of the infarction.

The Göteborg Metoprolol Trial[3] represented a step forward in assessing intervention begun within a few hours of onset of symptoms of AMI. Early intravenous treatment followed immediately by an oral regimen was found to be safe, and there was a 36% lower mortality rate in the metoprolol group compared with the placebo group after 90 days, a statistically significant difference. This relative mortality reduction was identical to that observed in the Norwegian Timolol Trial,[2] but in that late-entry study it was not achieved until 2 years after the start of treatment. This implies that more lives can be saved in a shorter period of time if the treatment is started immediately after arrival in a hospital.

There is still some uncertainty regarding whether the benefit:risk ratio during the in-hospital phase warrants the early start of treatment with β blockade in patients with suspected AMI. The MIAMI trial was designed to investigate this question further; the primary objective was to evaluate the effect of early intervention with metoprolol on hospital mortality.[4] Other important indexes of morbidity and tolerability were also evaluated. Based on a subgroup analysis of the Göteborg Metoprolol Trial,[4] the sample size was estimated to be adequate to detect a significant difference between treatments in mortality after 15 days.[5]

The MIAMI trial[6] aimed to select a group of patients with higher sympathetic activity but not already on treatment with β blockers or calcium-channel blockers, and this group was expected to have a placebo mortality of 7% after 15 days. The observed placebo mortality (4.9%) was considerably lower than predicted, and the difference between the treatment groups was 13% in favor of metoprolol—not statistically significant with a 95% confidence limit for the relative effect of metoprolol ranging from an 8% excess to a 33% reduction in mortality.[7]

These findings from the MIAMI trial have been combined with results from other early-entry studies with β blockers.[8] These data on nearly 14,000 patients indicate a difference of 10% in the in-hospital death risk with 95% confidence limits, ranging from an excess mortality of 5% to a 22% reduction in death risk. A recently completed study[9] of early intervention with atenolol in AMI patients found a 13% difference in total mortality after 7 days. When these data were pooled with those above,[8] there was a significant ($p = 0.03$) difference of 11% in the in-hospital death risk. The combined evidence in some 30,000 patients from these early-intervention studies suggests that even in relatively low-risk coronary care unit patients with an in-hospital mortality rate around 5%, early treatment with metoprolol can reduce early mortality.

A retrospectively designed multivariate analysis of the MIAMI mortality data indicated that there was a considerable proportion of patients at a low in-hospital death risk in whom a difference in mortality between treatment groups could not be detected.[7] There was an indication among the remaining patients that metoprolol had an increasing beneficial effect on mortality with increasing death risk.

It seems plausible that the heterogeneity in death risk among the MIAMI patients, with a preponderance of patients having a spontaneously benign course, may be a major reason that the overall difference between the treatments was not more pronounced.

The results of the MIAMI trial show that very early institution of metoprolol treatment can prevent infarct development and limit indexes of infarct size.[10,11] These effects are strongly dependent on delay time; the earlier treatment starts, the better the effect is. Patients with a higher sympathetic tone also seem to benefit more. These findings are in agreement with the observations from metoprolol[12–15] and other β blocker studies[16–19] concerning effects on indexes of infarct size.

From the Göteborg Metoprolol Trial,[20] the lower requirement for furosemide in the metoprolol-treated patients is supportive evidence that metoprolol limited the evolution of myocardial necrosis and reduced the severity of congestive heart failure. Again, that effect was inversely related to delay time. No differ-

ence in the mean dosages of furosemide was detected between the treatment groups in the MIAMI trial, in which many more patients were given furosemide.[21]

The incidence of a recurrent infarction during the study period was lower in the Göteborg Metoprolol Trial[3] (days 4 to 90) and tended to be lower in the MIAMI trial[9] (days 4 to 15). Prophylactic treatment has also been shown to prevent recurrent infarction in late-intervention studies.[1,2,22,23] It seems reasonable to believe that similar pathophysiologic mechanisms are involved in the development of the very first infarction and the reinfarction and that both events are favorably influenced by metoprolol.

Beta blockers are well established in the treatment of patients with angina pectoris to prevent pain and improve work capacity. The Göteborg Metoprolol Trial[12,14,24] showed that early institution of metoprolol in suspected AMI patients reduced ongoing chest pain and elevated ST segment, prevented recurrent chest pain and reduced the need of analgesics during the initial hospital phase. The MIAMI trial[25] supports these findings, showing a lower requirement for narcotic analgesics and other antianginal drugs, and a shorter duration of pain among metoprolol-treated patients.

Several studies have indicated that β blockers can reduce supraventricular as well as ventricular arrhythmias in patients with AMI.[16,26,27] The Göteborg Metoprolol Trial[28] showed a marked reduction of both types of arrhythmias and of the need of antiarrhythmic agents and digitalis during the hospital phase. Metoprolol treatment clearly prevented ventricular fibrillation and ventricular tachycardia.[28] In the MIAMI trial,[29] metoprolol treatment reduced the incidence of supraventricular tachyarrhythmias and the need for digitalis and other antiarrhythmic agents, but did not significantly affect the number of patients who developed ventricular fibrillation or ventricular tachycardia. Again, there were important differences between the 2 studies. In MIAMI there was a higher use of concomitant prophylactic antiarrhythmic medications; these were possibly given to patients at a high risk of developing ventricular fibrillation, because the incidence of ventricular fibrillation in the placebo group was only about half the incidence in the Göteborg Metoprolol Trial.

Favorable effects on early ventricular fibrillation have also been obtained with propranolol.[30] The fact that metoprolol,[23] propranolol[2] and timolol[1] in late-entry studies have shown a marked prophylactic effect against sudden cardiac deaths supports the idea that these β blockers are effective in preventing ventricular fibrillation.

Drug tolerance has been good in the long-term studies.[1,2] In the Göteborg Metoprolol Trial[3] tolerance was also good when metoprolol was injected intravenously early in the course of an AMI when patients were likely to be hemodynamically labile. Anxiety has persisted, however, regarding the safety and tolerability of intravenous β blockade in such patients. The MIAMI trial, based on close to 3,000 patients actively treated, firmly establishes that intravenous administration of metoprolol is safe when standard contraindications are observed.[21,31] It should also be stressed that patients with basal pulmonary rales were involved. The findings from the hemodynamic subgroup[32] of the MIAMI trial show that high left ventricular filling pressure is not further elevated by metoprolol during the 24 hours after the start of treatment. Similarly atrioventricular conduction was not seriously impaired by treatment.

The MIAMI trial patients were selected from the segment of all coronary care unit admissions having heart rate and blood pressure levels in the upper parts of the total distribution and were therefore not representative of all patients. They were not previously treated with β blockers. The actually observed global mortality difference was 13% from a 4.9% placebo mortality level. Thus, the MIAMI trial failed to refute the null hypothesis most probably because of a loss of statistical power. This might be due to the inclusion of a large proportion of patients with a spontaneously benign course and low mortality. This notion is supported by the multivariate analyses showing that as the placebo mortality increases to around 7% in segments of the study sample, the mortality reduction increases to about 30%. The question regarding the possibility of lowering the very early mortality in myocardial infarction by metoprolol treatment is not yet completely resolved. However, the confidence interval around the MIAMI mortality result includes that of the Göteborg Metoprolol Trial.

The final decision regarding choice of treatment in patients with AMI must be based on a global assessment of as many drug effects as possible. Early treatment with metoprolol, starting with an intravenous loading dose, seems to be indicated for a substantial proportion of patients admitted to coronary care units.

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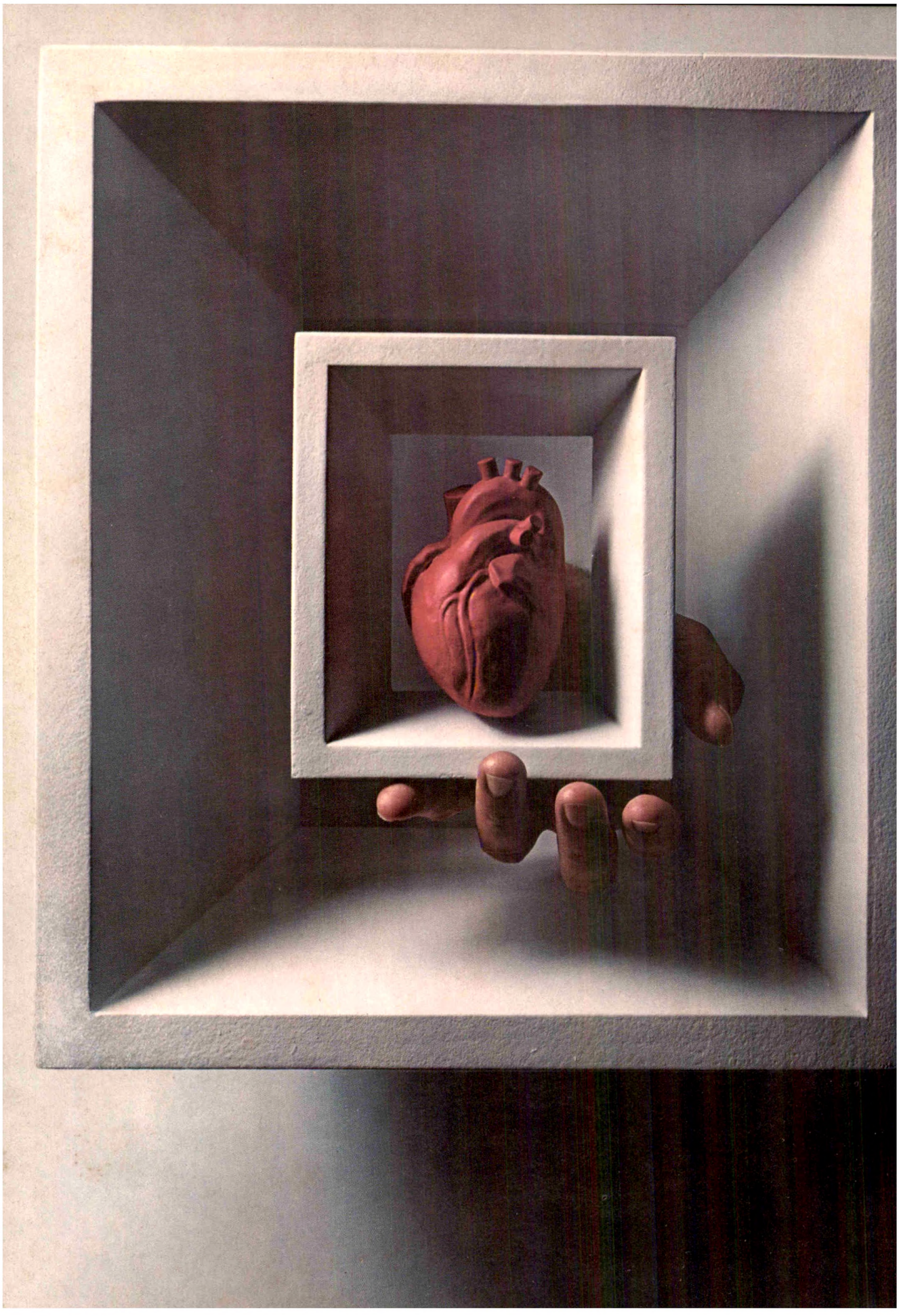

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hyorochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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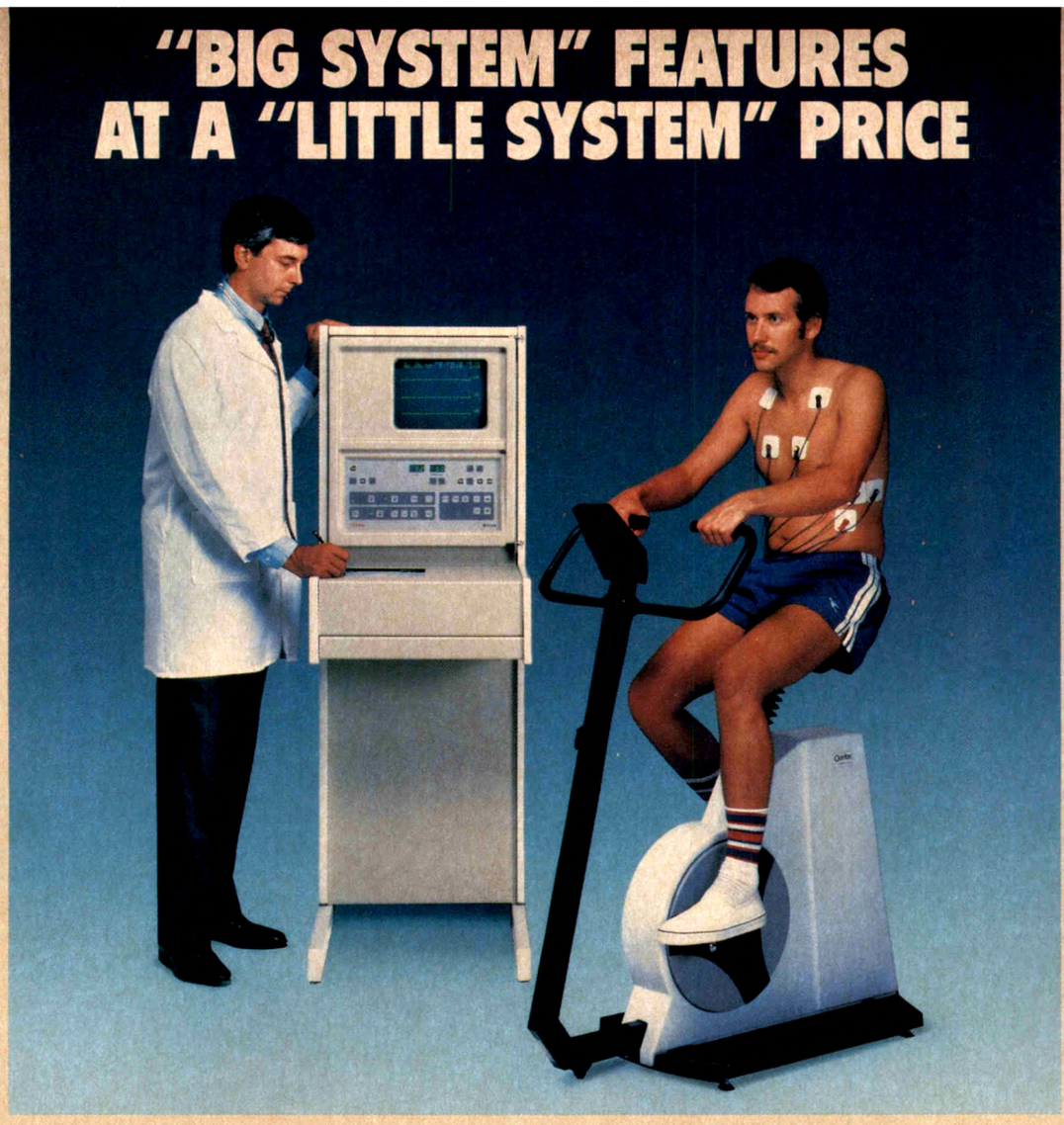

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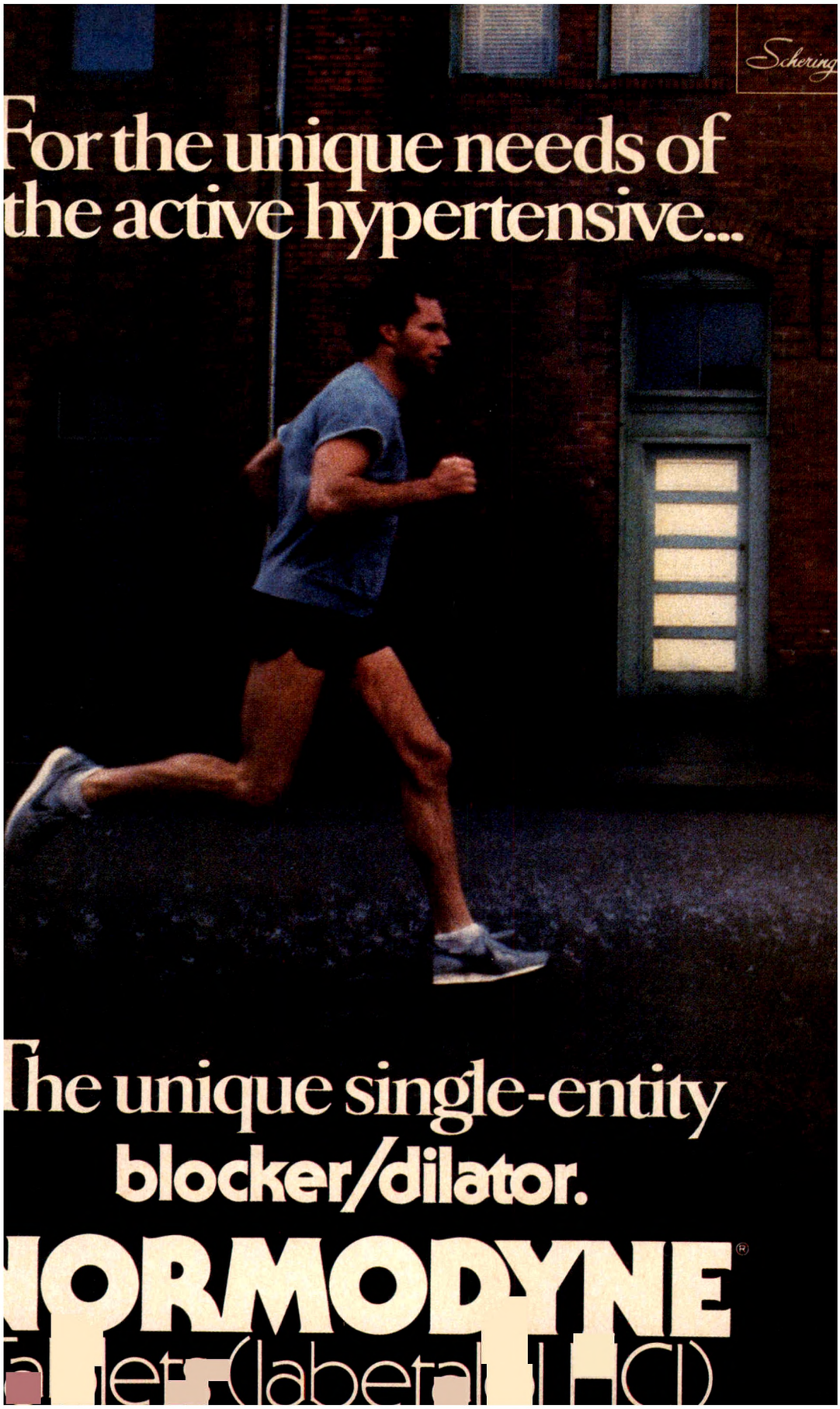
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PRODUCT INFORMATION

NORMODYNE®

brand of labetalol hydrochloride

Tablets

BRIEF SUMMARY

INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS

Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

PRECAUTIONS

General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600
Number of Patients	522	181	606	608
Dizziness (%)	2	3	3	3
Fatigue	2	1	4	4
Nausea	<1	0	1	2
Vomiting	0	0	<1	<1
Dyspepsia	1	0	2	1
Paresthesias	2	0	2	2
Nasal Stuffiness	1	1	2	2
Ejaculation Failure	0	2	1	2
Impotence	1	1	1	1
Edema	1	0	1	1

Labetalol HCl Daily Dose (mg)	800	900	1200	1600	2400
Number of Patients	503	117	411	242	175
Dizziness (%)	5	1	9	13	16
Fatigue	5	3	7	6	10
Nausea	4	0	7	11	19
Vomiting	<1	0	1	2	3
Dyspepsia	1	0	2	2	4
Paresthesias	1	1	2	5	5
Nasal Stuffiness	2	2	4	5	6
Ejaculation Failure	3	0	4	3	5
Impotence	2	4	3	4	3
Edema	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes Dry eyes.

Immunological System Antimitochondrial antibodies.

Liver and Biliary System Cholestasis with or without jaundice.

Musculo-Skeletal System Muscle cramps; toxic myopathy.

Respiratory System Bronchospasm.

Skin and Appendages Rashes of various types, such as generalized maculo-papular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block. See **CONTRAINDICATIONS.**

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a $beta_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered three times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED

NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).

NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.

For complete prescribing information, please consult package insert.

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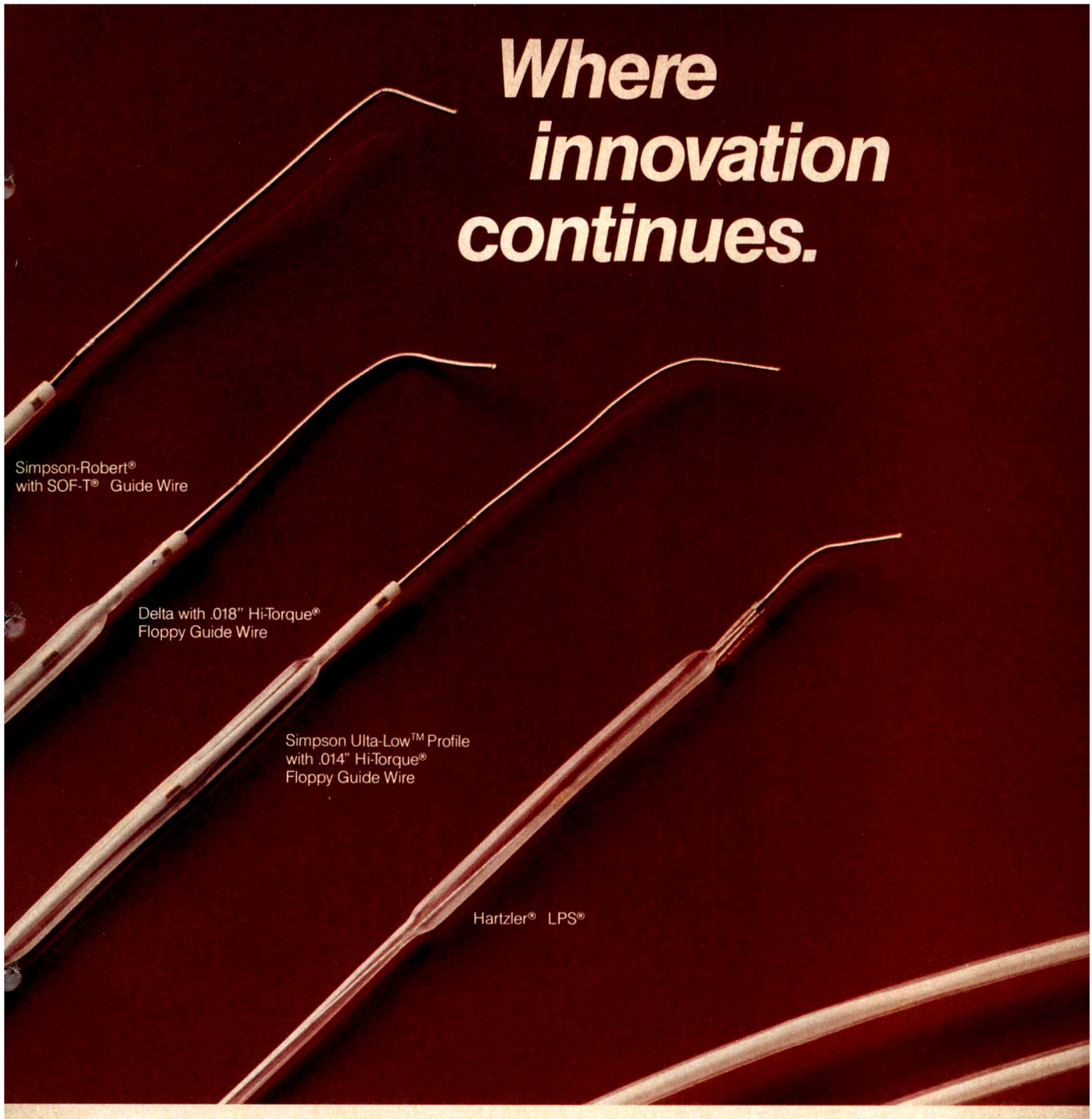

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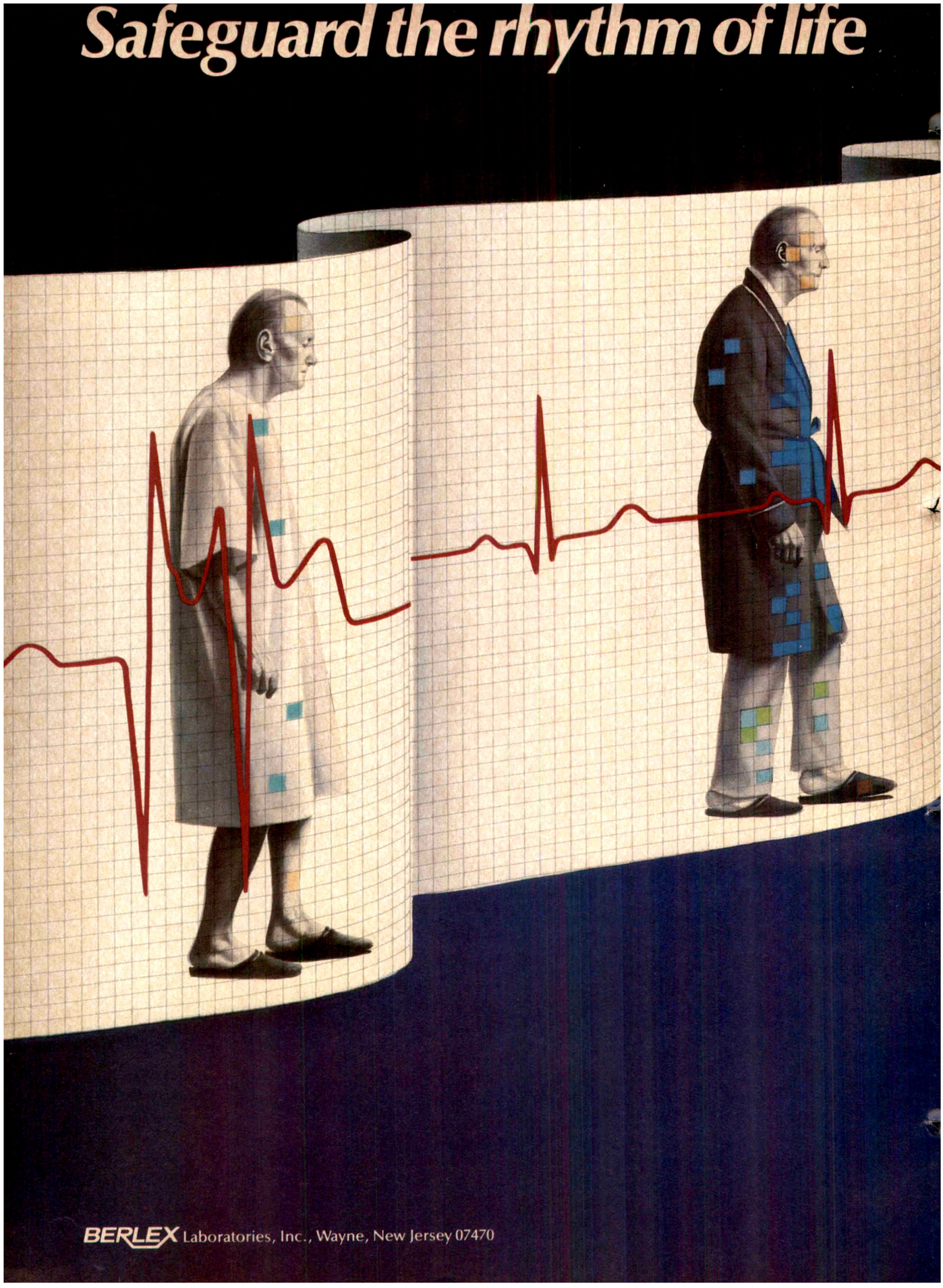

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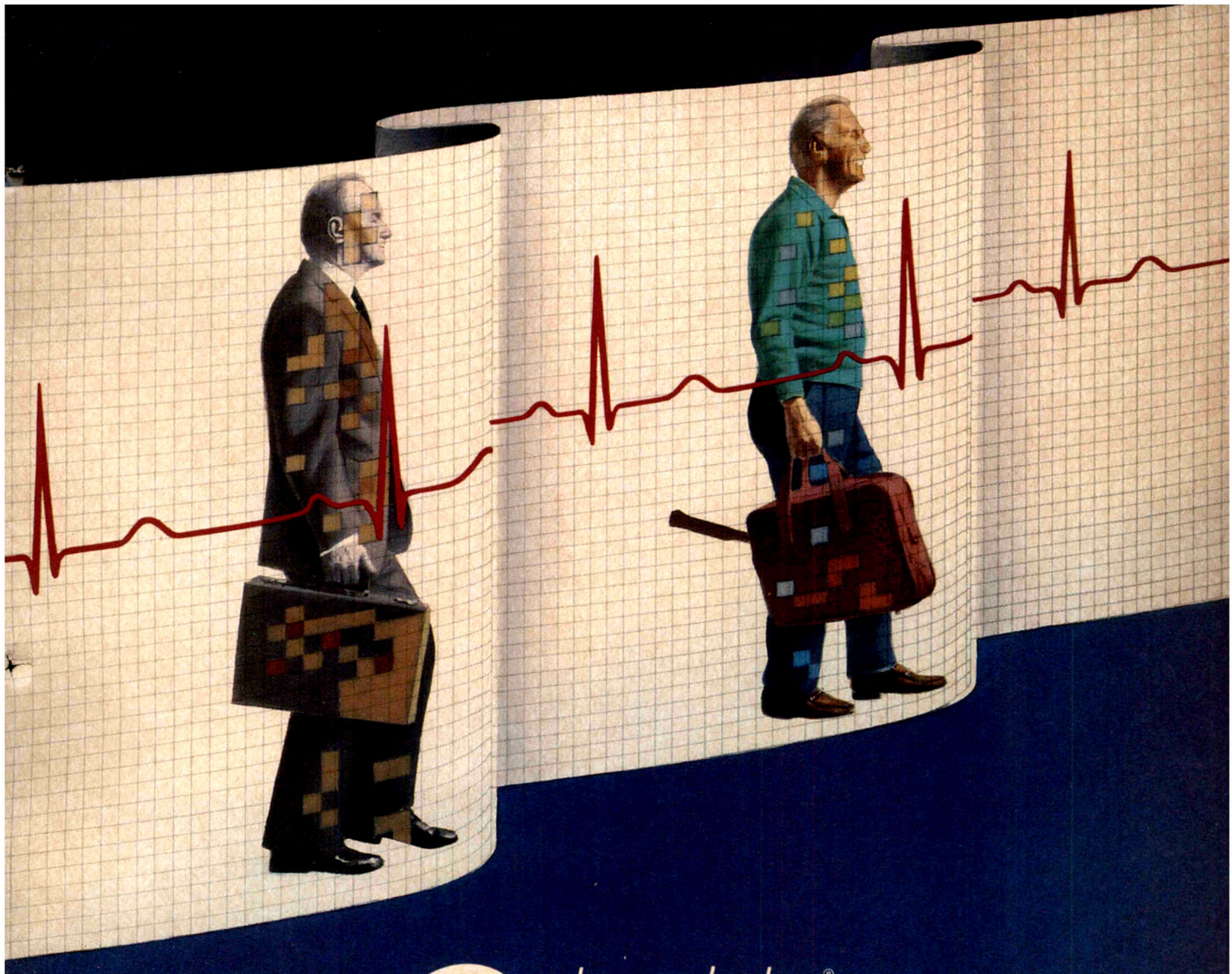

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- Continuous arrhythmia control
- Well tolerated in long-term therapy[1]
- Less GI upset than with quinidine sulfate[2]
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Start the oral agent he can live with

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2. Podrid P: *Patient Care* 1981;15:100-132.

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1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock)
2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia atrial flutter, atrial fibrillation (chronic and paroxysmal).
CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.
WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine. 2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered. 3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring. 4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals. 5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication. 6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity. 7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal. 8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.
PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk. *Information for Patients:* As with all solid oral medications, Quinaglute (quinidine gluconate) Dura-Tabs (sustained-release tablets) should be taken with an adequate amount of fluid, preferably in an upright position, to facilitate swallowing.

Drug Interactions: *Drug*	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinaglute (quinidine gluconate) Dura-Tabs should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.
Nursing Mothers: Caution should be exercised when Quinaglute (quinidine gluconate) Dura-Tabs are administered to a nursing woman due to passage of the drug into breast milk.
Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinaglute (quinidine gluconate) Dura-Tabs in children.
ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.
Less frequently encountered adverse reactions:
Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.
Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.
Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.
Dermatologic: Rash, cutaneous flushing with intense pruritus, urticaria. Photosensitivity has also been reported.
Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although extremely rare, there have also been reports of lupus erythematosus in patients taking quinidine. A positive association with quinidine therapy has not been established.
See package insert for full information.

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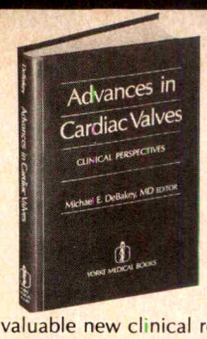
The Most Extensive Compilation of Information on Heart Valve Replacement Available Today!



Advances in Cardiac Valves
Clinical Perspectives

edited by
Michael E. DeBakey, MD
0-914316-40-0, 1983, 274pp., $35.00

This valuable new clinical reference provides a detailed update on many aspects of mechanical heart valve prostheses, including hemodynamics, clinical results, results in children, non-invasive assessments, special indications, and implant techniques. Each topic is presented in an easily understood style and format which facilitate the comprehension of recent developments in heart valve replacement for the busy clinician.

Each chapter is written by internationally respected physicians and medical scientists each of whom is pre-eminent in his field. All of the information has been co-ordinated by Dr. DeBakey to produce a very readable and informative volume on the state-of-the-art of heart valve replacement with mechanical prostheses. No cardiologist, cardiovascular surgeon, internist, or bioengineer can afford *not* to be knowledgeable about the information in this book.

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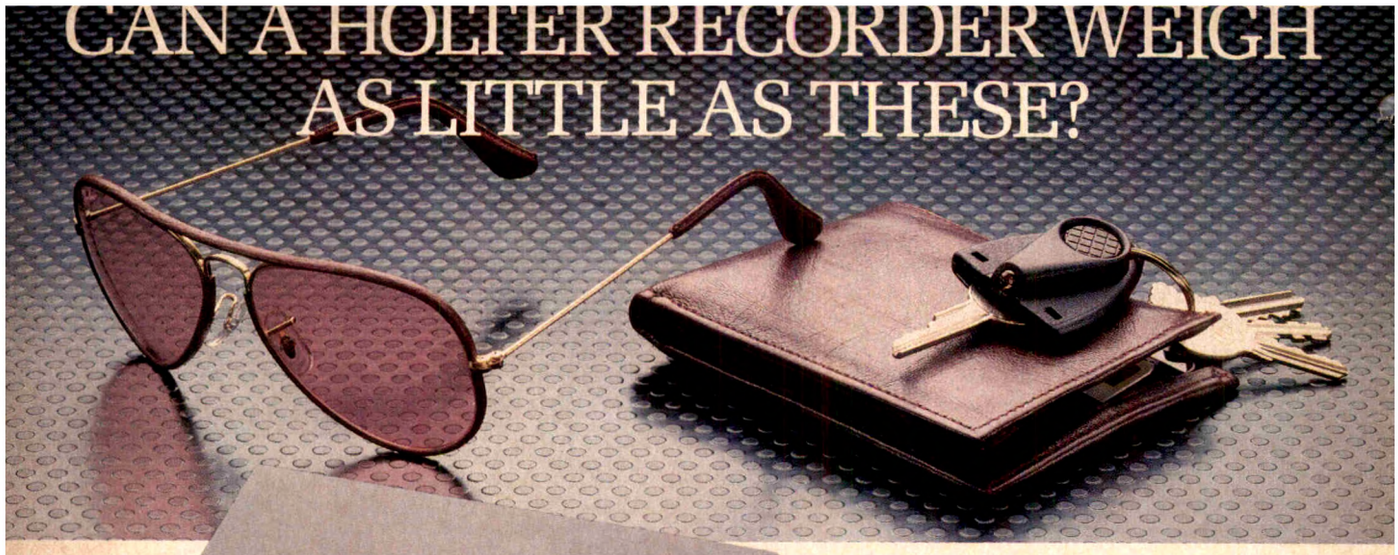

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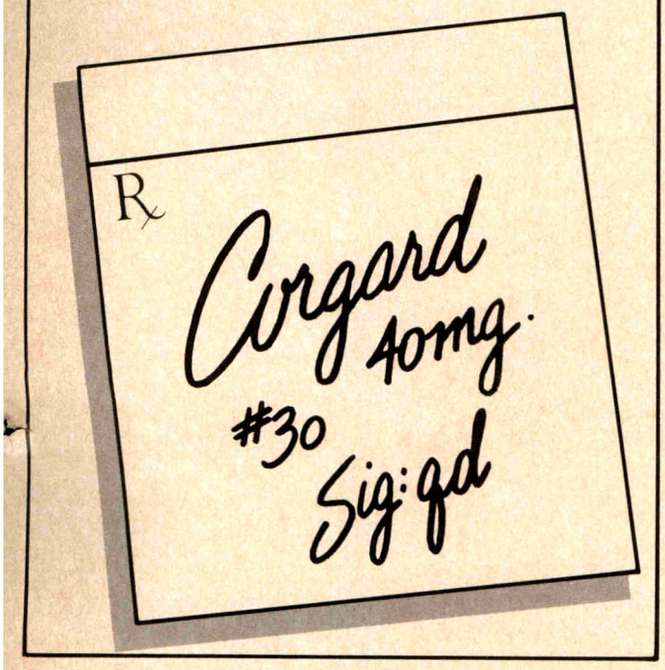

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy—In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia. The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg q.d. (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg q.d. (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

References: 1. Alexander JC, et al: Long-term experience with nadolol in the treatment of hypertension and angina pectoris. Am Heart J October Supplement 108 (4):1136-1140, 1984. 2. Data on file, Squibb Institute for Medical Research.

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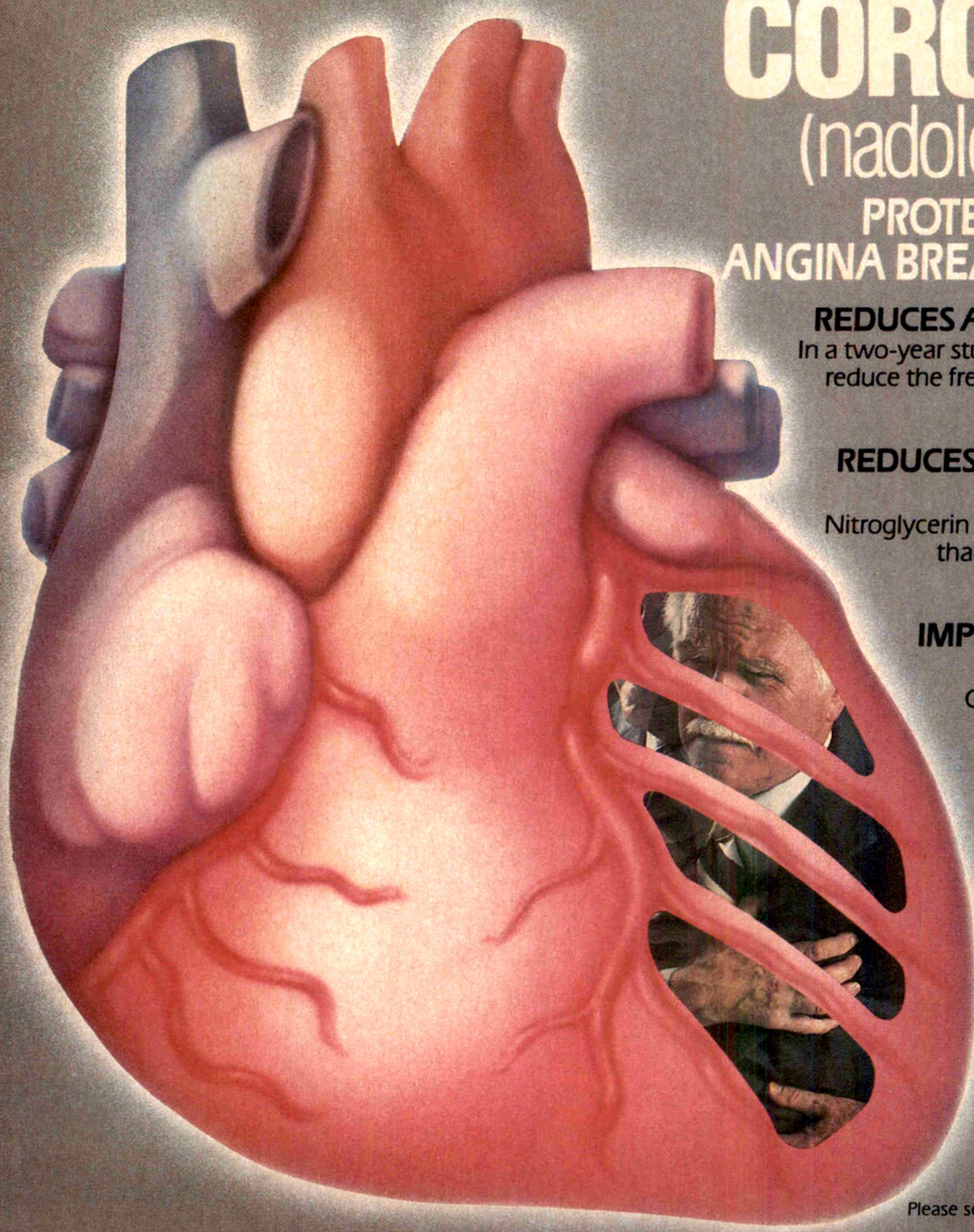

*The syndrome of recurring symptoms compounded by the fear of impending attacks.

Please see brief summary of prescribing information on adjacent page.

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SYSTEMIC HYPERTENSION

913 **Systolic Hypertension in the Elderly Program (SHEP): Antihypertensive Efficacy of Chlorthalidone**

STEPHEN B. HULLEY, CURT D. FURBERG, BARRY GURLAND, ROBERT McDONALD, MITCHELL PERRY, HAROLD W. SCHNAPER, JAMES A. SCHOENBERGER, W. McFATE SMITH, and THOMAS M. VOGT, *for the* SHEP RESEARCH GROUP

Men and women who had isolated systolic hypertension and were at least 60 years old were treated for 1 year with chlorthalidone (25 to 50 mg/day) or matching placebo as the step I drug. Most patients reached goal blood pressure (BP) without requiring a step II drug. The BP response was similar in all age, sex and race subgroups, with an overall difference between the randomized groups of 17 mm Hg for systolic BP ($p < 0.001$) and 6 mm Hg for diastolic BP ($p < 0.001$). The only common adverse effects were asymptomatic changes in the serum levels of potassium (0.5 mEq/liter lower in the chlorthalidone group, $p < 0.001$), uric acid (0.9 mg/dl higher, $p < 0.001$) and creatinine (0.08 mg/dl higher, $p = 0.02$). Compliance was good; more than 80% of the participants were still taking study medications at the end of the year.

921 **Doppler Evaluation of Left Ventricular Diastolic Filling in Children with Systemic Hypertension**

A. REBECCA SNIDER, SAMUEL S. GIDDING, ALBERT P. ROCCHINI, AMNON ROSENTHAL, MACDONALD DICK II, DENNIS C. CROWLEY, and JANE PETERS

To assess left ventricular (LV) diastolic function in systemic hypertension, 11 children with systemic hypertension and 7 normal children underwent M-mode echocardiography and Doppler ultrasound examination of LV inflow. Echocardiographic diastolic relaxation times and filling rates and Doppler diastolic time intervals did not distinguish normal subjects from patients with hypertension. Analysis of the mitral valve Doppler recordings of the patients with hypertension showed an increased peak velocity during atrial contraction (A wave), an increased area under the A wave, a decreased percent of the total area of the mitral valve Doppler waveform in the first one-third of diastole, and an increased percent of the total area of mitral valve Doppler waveform under the A wave compared with that in normal subjects. These findings suggest a relative shift in LV filling toward the latter part of diastole in children with mild systemic hypertension probably caused by altered diastolic compliance.

927 **Systemic Hypertension After Cardiac Transplantation: Effect of Cyclosporine on the Renin-Angiotensin-Aldosterone System**

MARC BELLET, CHRISTIAN CABROL, PAOLO SASSANO, PHILIPPE LÉGER, PIERRE CORVOL, and JOËL MÉNARD

Fifteen hypertensive cardiac transplantation patients (13 of whom were normotensive before transplantation) were treated with cyclosporine. No resulting abnormalities were observed in plasma renin, angiotensinogen or converting enzyme activity, and the level of plasma aldosterone was normal. However, 2 abnormalities

Continued on page A20

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Clinical Clues to MIXED ANGINA *No. 5*

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Most days she can climb the stairs with no difficulty. But today she was less than half-way up when an angina attack stopped her.

That's the unpredictability of MIXED ANGINA—vasoconstriction coexisting with fixed coronary lesion, to produce a critical reduction of myocardial blood flow.

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- at varying levels of exercise
- at rest, or even during sleep
- upon exposure to cold
- under emotional stress
- diurnally, typically in the morning

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As a result, PROCARDIA can significantly reduce your patient's angina attack rate and need for nitroglycerin.[1]

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Primary Protection in
MIXED ANGINA

Please see PROCARDIA® (nifedipine) brief summary on next page.

The stairs seem steeper today

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

PRIMARY PROTECTION IN MIXED ANGINA

Usual Effective Dosage: 30 to 60 mg/day

For most patients, titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases.

A Favorable Safety Profile

Most frequently reported side effects, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%.

Reference:

1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 106:644-652, 1983.

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well-documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA (nifedipine) therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA patients. No clinical significance for these findings has been demonstrated.

Although PROCARDIA has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to PROCARDIA therapy is uncertain in most cases but probable in some.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, mice and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cramps, flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, gingival hyperplasia, and erythromelalgia. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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accompanied the increase in blood pressure after cyclosporine treatment: a rise in serum creatinine to values higher than those recorded before transplantation accompanied by low creatinine clearance and a slight increase in plasma volume. Nifedipine induced a larger acute decrease in blood pressure than captopril.

MISCELLANEOUS TOPICS

932 Ventricular Performance in Human Hearts Aged 61 to 73 years

J.V. NIXON, HUGH HALLMARK, KIM PAGE, PETER R. RAVEN, and JERE H. MITCHELL

To determine the response of the older left ventricle to large variations in preload, studies were carried out in 11 subjects, aged 61 to 73 years, who had been carefully screened to rule out latent coronary heart disease. Two-dimensional echocardiograms were recorded before and at the termination of 5 degrees of head-down tilt for 90 minutes and at the termination of graded lower body negative pressure to −40 mm Hg. The older left ventricle conformed to the normal ascending Frank-Starling curve, but compared with changes in younger subjects, showed an altered response to these variations in preload, suggesting an age-related change in diastolic stiffness.

938 Magnetic Resonance Imaging in Pulmonary Arterial Hypertension

ALAIN BOUCHARD, CHARLES B. HIGGINS, BENJAMIN F. BYRD III, EUGENIO G. AMPARO, LUCI OSAKI, and RICHARD AXELROD

Magnetic resonance imaging (MRI) displays the blood pool as very low or no signal intensity so cardiac structures can be visualized without contrast medium. Consequently, MRI was used to examine the right ventricle and pulmonary arteries (PAs) in 17 patients with PA hypertension documented by cardiac catheterization. The study population consisted of 7 patients with primary PA hypertension, 7 patients with Eisenmenger's syndrome and 3 patients with PA hypertension secondary to lung disease. The MRI studies of patients were compared with those from 10 normal volunteers. There was good correlation between end-diastolic right ventricular wall thickness and mean PA pressure ($r = 0.79$). MRI showed enlargement of PAs in all patients with PA hypertension. A magnetic resonance signal was present in the PAs throughout the cardiac cycle in patients with severe PA hypertension (more than 90 mm Hg) in contrast to the absence of signal during systole in normals. Signal within the PA vessels in systole is consistent with decreased flow velocity in patients with severe PA hypertension. MRI was useful in detecting each of the congenital anatomic defects in patients with Eisenmenger's syndrome.

943 Early Cardiac Changes Related to Radiation Therapy

MARKKU J. IKÄHEIMO, KARI O. NIEMELÄ, MARKKU M. LINNALUOTO, MATTI J.T. JAKOBSSON, JUHA T. TAKKUNEN, and PENTTI J. TASKINEN

In 21 women without cardiac disease, postoperative radiation therapy for breast cancer was associated with a transient decrease in left ventricular function measured by echocardiography and systolic time intervals. These changes became normalized within 6 months after therapy. Up to 6 months after therapy, a slight pericardial effusion was found in 33% of the patients.

METHODS

947 Reproducibility of Left Ventricular Area and Volume Measurements Using a Computer Endocardial Edge-Detection Algorithm in Normal Subjects

DONALD A. CONETTA, EDWARD A. GEISER, LESLIE H. OLIVER, ALAN B. MILLER, and C. RICHARD CONTI

A computer endocardial border-detection algorithm was used to determine left ventricular (LV) short-axis area in normal subjects. The LV areas, volumes, and area and volume ejection fraction (EF) were determined from 5 serial recordings in 10 normal subjects in 2 separate echocardiographic laboratories during a 2-week study

Continued on page A24

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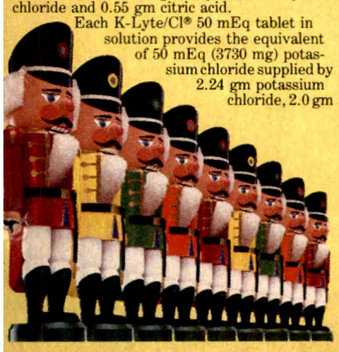
Each K-Lyte/Cl® 50 mEq tablet in solution provides the equivalent of 50 mEq (3730 mg) potassium chloride supplied by 2.24 gm potassium chloride, 2.0 gm potassium bicarbonate and 3.65 gm L-lysine monohydrochloride and 1.0 gm citric acid.



INDICATIONS AND USAGE: Therapy or prophylaxis of potassium deficiency.

CONTRAINDICATIONS: Contraindicated in patients with hyperkalemia. Hyperkalemia may complicate chronic renal impairment, metabolic acidosis, acute dehydration, and extensive tissue breakdown. Concomitant administration of potassium salts and potassium-sparing diuretic can produce severe hyperkalemia.

WARNINGS: In patients with impaired potassium excreting mechanisms, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and may be asymptomatic. Use in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. Acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of reduced total body potassium. Therefore, the treatment of potassium depletion requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the ECG, and the clinical status of the patient.

Information for Patients: Patients should be carefully directed to completely dissolve each tablet.

Drug Interactions: Simultaneous administration of potassium supplements and a potassium-sparing diuretic as well as concomitant use of potassium supplements and salt substitutes can result in hyperkalemia (see Contraindications).

Usage in Pregnancy - Pregnancy Category C: It is not known whether K-Lyte products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Nursing Mothers: There is a potential for serious adverse reactions in nursing infants from oral potassium supplements given to the mother. Nursing or the drug should be discontinued based on the importance of the drug for the mother.

Usage in Children: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: The most common adverse reactions to oral potassium supplements are nausea, vomiting, diarrhea and abdominal discomfort. These side effects occu more frequently when the medication is not taken with food or is not diluted properly or dissolved completely.

Hyperkalemia occurs only rarely in patients with normal renal function receiving potassium supplements orally.

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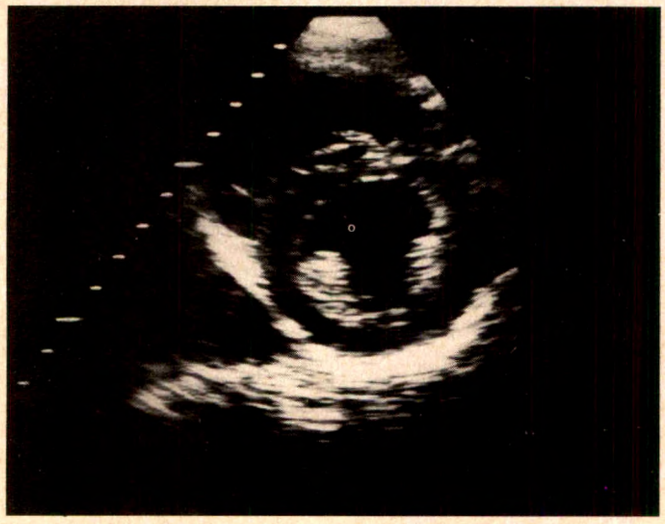

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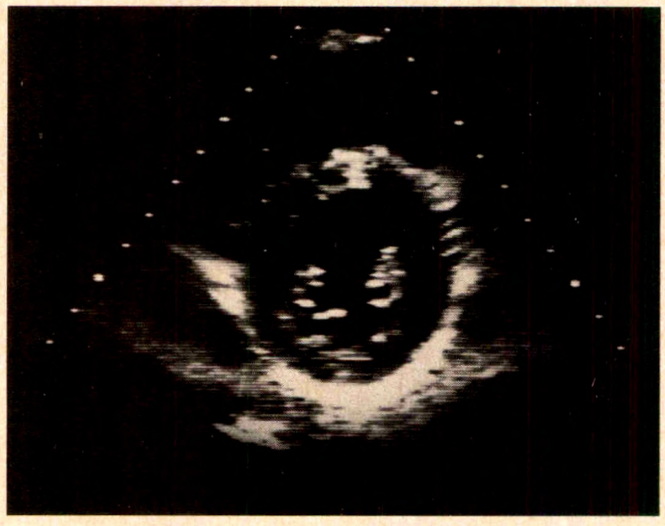

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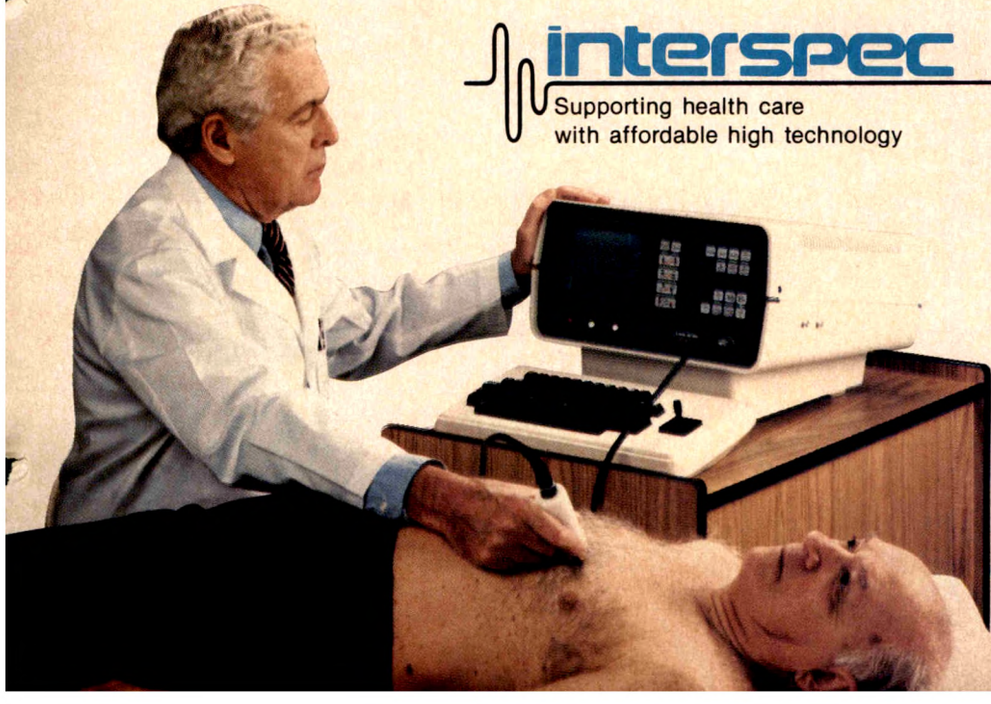

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period. The area and volume data were statistically analyzed to provide individual and group 95% confidence limits for determining the percent difference between serial, end-systolic and end-diastolic areas and volumes, area and volume EF. The limits for end-diastolic volume (±16.7%) were similar to, while those for end-systolic volume (±17%) and volume EF (±9.7) were narrower than, those previously recorded. This computer analysis of echocardiographic LV indexes may provide a more sensitive method for detecting change of serially recorded echoes in patients.

953 Nd-YAG Laser Fusion of Human Atheromatous Plaque-Arterial Wall Separations in Vitro

JOHN F. HIEHLE Jr., DONNA B.C. BOURGELAIS, STANLEY SHAPSHAY, FREDERICK J. SCHOEN, DUCKSOO KIM, and J. RICHARD SPEARS

The efficacy of a new technique, laser balloon angioplasty, for treatment of arterial dissections was tested in human postmortem atherosclerotic arteries. Separated layers of plaque and underlying arterial wall were juxtaposed and 17 W of neodymium-yttrium aluminum garnet laser radiation were directed perpendicularly to the luminal surface for 5 to 32 seconds over a nominal spot size of approximately 4 mm^2. Depending on lasing duration, satisfactory tissue welds (supporting loads up to 25 g) could be achieved when external pressure was applied to the tissues during lasing and when blood was present within the dissected plane. This technique was also successfully applied during postmortem balloon angioplasty with a prototype balloon within which a laser-transmitting optical fiber terminated in a diffusing tip for lateral dispersion of laser energy. The improved luminal geometry afforded by application of this catheterization technique may be useful for treatment of spontaneous and balloon angioplasty–induced arterial dissections.

CARDIOVASCULAR PHARMACOLOGY

958 Circulatory Effects of Coffee in Relation to the Pharmacokinetics of Caffeine

PAUL SMITS, THEO THIEN, and ALBERT van't LAAR

In 8 normotensive subjects, circulatory parameters were studied after intervention with coffee in 2 strengths, decaffeinated coffee and hot water after a caffeine abstinence of 4.5 times the individual caffeine half-life. Drinking regular and strong coffee resulted in a similar increase in systolic and especially in diastolic blood pressure (±15%), whereas increases in forearm blood flow and plasma epinephrine were less pronounced. After ingestion of decaffeinated coffee, a small increase in diastolic blood pressure was seen, and after drinking water no changes were observed. In another group of 30 normotensive subjects, a negative correlation was ascertained between the coffee-induced increase in blood pressure and basal plasma caffeine level ($r = -0.71$, $p < 0.001$). It is concluded that with chronic caffeine intake during daily life, subjects in whom the plasma caffeine half-life is short are exposed to a pressor response after drinking coffee despite the phenomenon of adaptation as described in published reports.

EXPERIMENTAL STUDIES

964 Beta-Adrenergic Stimulation Reverses Postischemic Myocardial Dysfunction Without Producing Subsequent Functional Deterioration

ROBERTO BOLLI, WEI-XI ZHU, MARY LEE MYERS, CRAIG J. HARTLEY, and ROBERT ROBERTS

The prolonged myocardial dysfunction observed after reversible ischemia (stunned myocardium) has been attributed to inability of myocytes to replenish ATP stores. Accordingly, inotropic stimulation should produce little or no increase in function. To test this hypothesis, systolic wall thickening, an index of regional myocardial function, was measured ultrasonically in open-chest dogs undergoing 15 minutes of occlusion of the left anterior descending coronary artery (LAD) followed by 4 hours of reperfusion. Three hours after reperfusion, function in the LAD-dependent territory was still severely depressed (12.3 ± 16.1% of baseline). Isoproterenol (0.1 mg/kg/min intravenously) increased function to values similar to baseline. Discontinuation of isoproterenol was associated with return of function to pre-isoproterenol levels. Thus, stunned myocardium responds dramatically to β-adrenergic stimulation without subsequent adverse effects on function in the short term. The data indicate that stunned myocardium is inherently capable of generating ATP and do not support the view that an inability to replenish ATP stores causes postischemic dysfunction.

Continued on page A33

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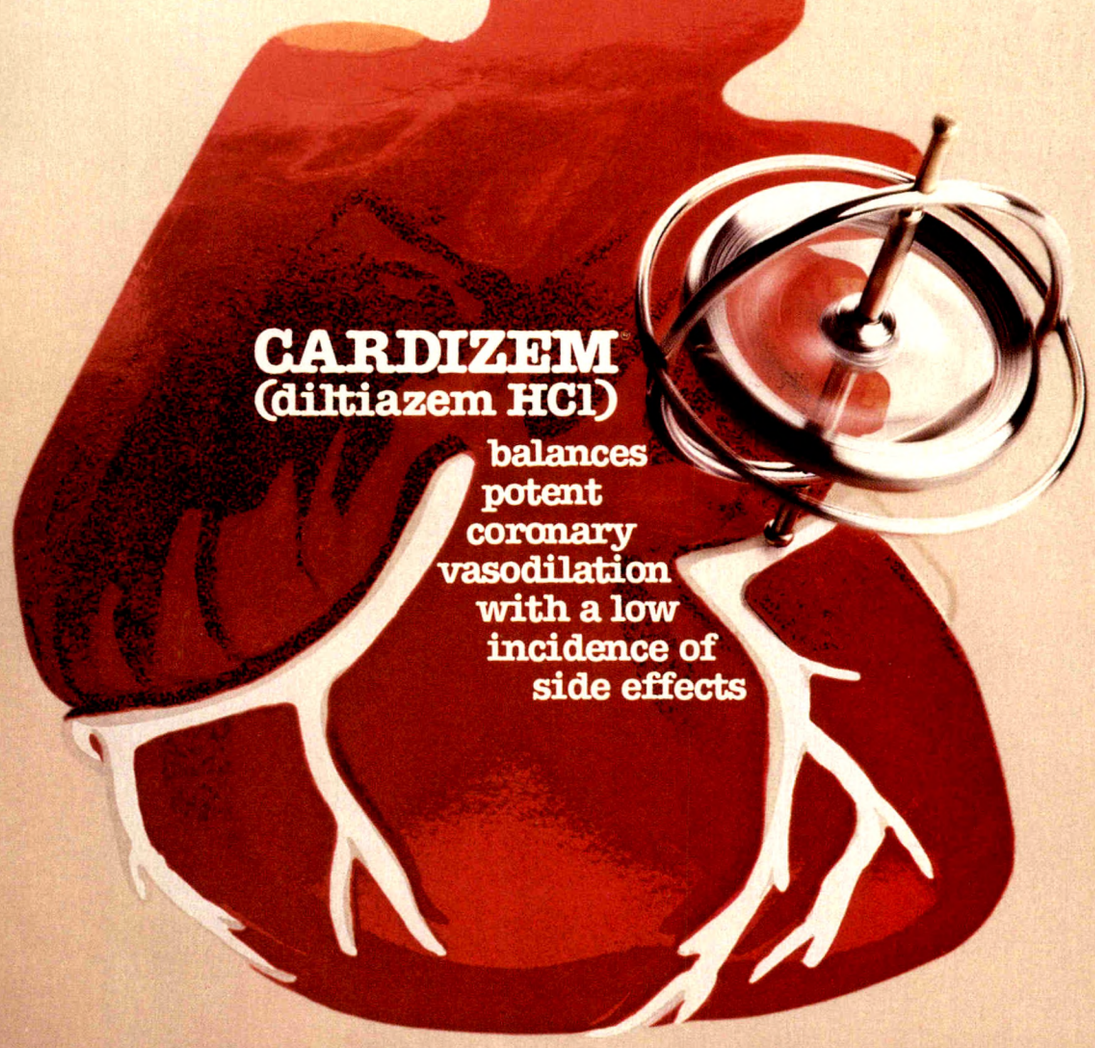

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References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

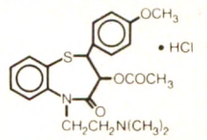
2/84

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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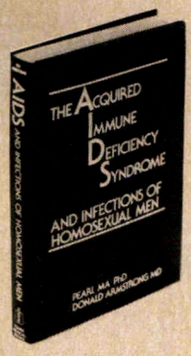

From the Publishers of The American Journal of Medicine, The American Journal of Surgery, and Cutis

Acquire Immune Deficiency Syndrome (AIDS) and Infections of Homosexual Men

edited by **Pearl Ma, PhD,** and **Donald Armstrong, MD** with a foreword by **David J. Sencer, MD,** *Commissioner of Health, New York City; formerly Director, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services*
0-914316-38-9, 442 pages, illus., 1984, $39.50

The first scientific presentation to review all the facts in full

AIDS has become one of the most publicized diseases in modern times. It has produced fear and confusion in the general public and presented a formidable challenge to the medical community. Physicians and scientists have begun work on managing this epidemic, disease control centers continue to search for answers, and the federal government has declared AIDS the number one health priority of the nation. Understanding this disease demands cooperation between many different medical specialties, and papers on this subject have been published in many diverse journals not regularly read by individual specialists. Now, for the first time, two highly distinguished medical experts, Drs. Pearl Ma and Donald Armstrong, have coordinated in one easily accessible volume the complete range of interdisciplinary approaches to this complex disease, with contributions by the most eminent researchers and physicians in disease control and hospital teaching centers throughout the country. Comprehensive coverage is given to the entire spectrum of sexually transmitted diseases, and an additional section on diagnostic perspectives offers never before published material on why this syndrome occurs primarily among homosexual men. For any physician or other health care professional interested in the prevention and cure of this modern epidemic, this book is an indispensable guide to recognizing and treating AIDS and other sexually transmitted diseases.

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BRIEF SUMMARY

INDICATIONS—Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency of, or eliminate, anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack. Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.
PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.
ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.
DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25, 50 and 75 mg. For complete details, please see the full prescribing information.

PE 3026 7/84 – 2

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Cardiac Bioprostheses

Proceedings of the Second International Symposium
Rome, Italy, May 17-19, 1982

The most up-to-date presentation of the latest data on the entire range of clinical, bioengineering, pathology, and long-range follow-up issues on cardiac tissue valves.

edited by Lawrence H. Cohn, MD, and Vincenzo Gallucci, MD
ISBN 0-914316-34-6, 609pp., illus., 1982, $69.00

An international program committee organized this symposium on a strictly competitive abstract basis. It was held less than six months ago. One-hundred-eighty abstracts were submitted and 45 in 8 categories were accepted. Virtually every major cardiovascular center in the world that has any meaningful experience with cardiac bioprosthetic valves was represented. Nowhere will you find between two covers as much **current** information on the field of cardiac valves.

Almost 20 years have gone by since the first reports of homograft valve replacement by Drs. Donald Ross and Brian Barratt-Boyes and almost 10 years since the first reports began to appear about commercially available, quality-controlled porcine bioprosthetic and bovine pericardial valves. This book brings you completely up-to-date on what has happened since and what is happening **today.**

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Who are the editors?

Lawrence H. Cohn, MD, is Professor of Surgery, Harvard Medical School, and Cardiothoracic Surgeon, Brigham and Womens' Hospital. He is the author of **Modern Techniques in Surgery** and co-author of the new annual, **Cardiology,** now available in its second issue, **Cardiology 1982.**

Vincenzo Gallucci, MD, is Professor of Cardiovascular Surgery, Departments of Cardiovascular Surgery and Cardiology, University of Padova Medical School, Padova, Italy.

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All qualified individuals are encouraged to apply, but preference will be given to Canadian citizens and permanent residents. Deadline for receipt of applications is December 31, 1985.

Please send curriculum vitae and the names of three referees to:

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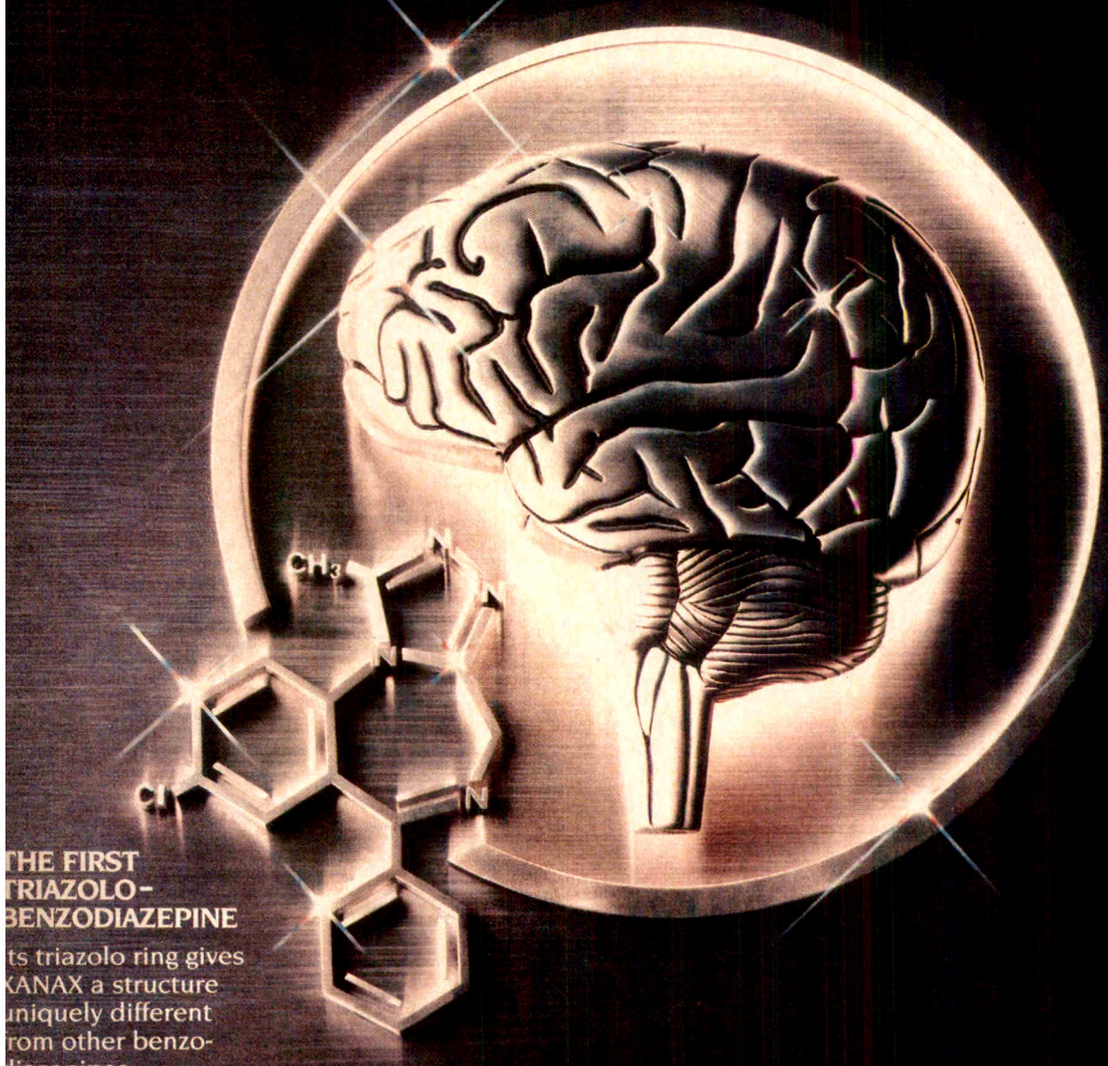

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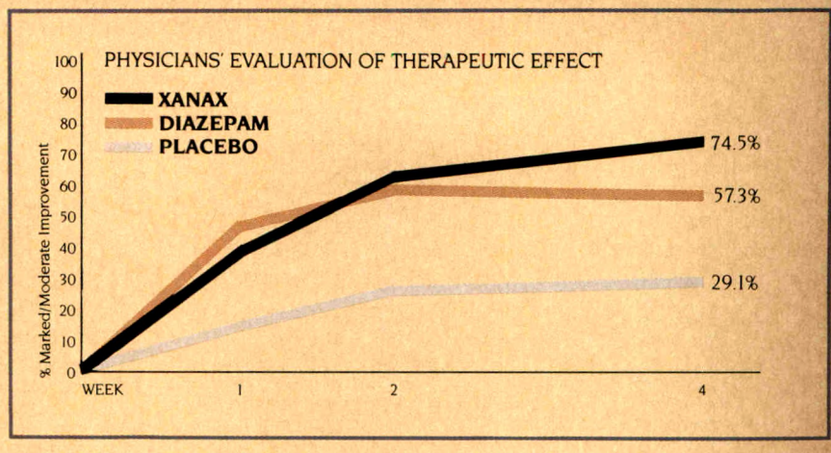
In double-blind, placebo-controlled clinical trials in 976 patients with moderate to severe clinical anxiety, therapy with XANAX was compared to diazepam.*

Patients treated with XANAX *had a significantly lower incidence of drowsiness when compared directly to diazepam* therapy in *a 976-patient*, placebo-controlled, multicenter study.*

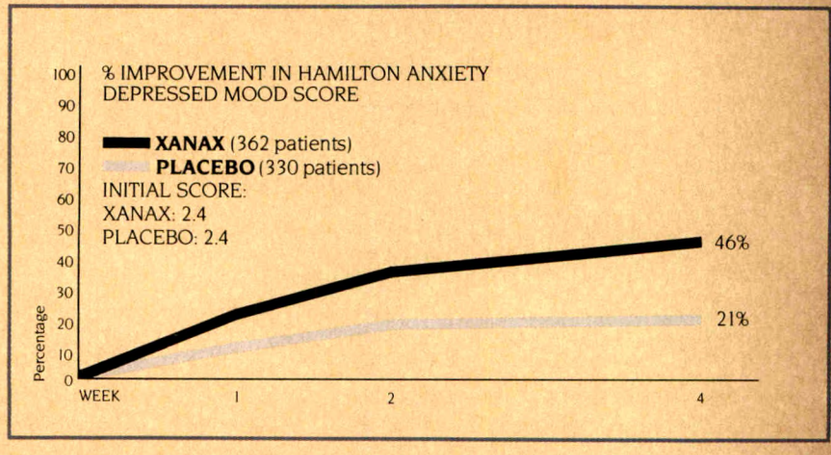


AND CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

EFFECTIVE IN CLINICAL ANXIETY WITH DEPRESSIVE SYMPTOMS

Patients with clinical anxiety may complain of having feelings of depression, such as sadness, blueness, or loneliness.

Depressed mood is one of 14 items on the Hamilton Anxiety Rating Scale. Special analysis of 692 anxious patients with a significant depressed mood item score showed that treatment with XANAX was significantly better than placebo in decreasing depressed mood score.



SIMPLE DOSAGE: XANAX 0.25–0.5 mg T.I.D.

The usual starting dose of XANAX is 0.25 to 0.5 mg, three times daily.

Please see next page for brief summary of prescribing information.

Xanax® 0.5 mg Tablets

alprazolam Ⓒ IV

XANAX® Tablets
(alprazolam)

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-3-S

*Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. J Clin Psychiatry 42 (9):347-351, 1981.

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969 Myocardial Kinetics of Thallium-201 After Stress in Normal and Perfusion-Reduced Canine Myocardium
ROBERT D. OKADA

Eleven mongrel dogs with experimental left anterior descending coronary stenoses were given thallium during norepinephrine infusion to simulate exercise. The infusion was then discontinued and thallium activity monitored regionally using miniature radiation detectors for 3 hours. The mean fractional myocardial thallium clearance was lower (0.47 ± 0.03 [± standard error of the mean]) for the stenosis zone compared to the no-stenosis zone (0.57 ± 0.03) ($p < 0.0001$). The stress blood flow ratio (stenosis/no-stenosis zone = 0.27 ± 0.06) was significantly lower than the final thallium activity ratio (0.68 ± 0.07) ($p < 0.001$), consistent with thallium redistribution occurring over the 3-hour period. In conclusion, myocardial thallium kinetics has been described in an exercise-simulated dog model. The fractional clearance of thallium can differentiate myocardium distal to a coronary vessel stenosis from that supplied by a normal coronary vessel.

974 Relation of Myocardial Salvage to Size of Myocardium at Risk in Dogs
ANDREW ZALEWSKI, SHELDON GOLDBERG, DUARTE B. FARIA, RICHARD KROL, and PETER R. MAROKO

The relation between the size of myocardium at risk and the magnitude of myocardial salvage with different pharmacologic interventions was studied. Open-chest, anesthetized dogs underwent left anterior descending coronary artery occlusion; 15 minutes after ligation they were treated with 5 different pharmacologic interventions. Retrospectively, the dogs were separated into 2 subgroups: those with small risk area, i.e., more than 15% of the left ventricle, and those with large risk area, i.e., more than 15% of the left ventricle. Heart rate and mean arterial pressure were similar between the 2 groups throughout the 6-hour experiments. In the subgroup with a small risk area, significantly more myocardium was salvaged than in the subgroup with large risk area. There was a close inverse correlation between the size of the area at risk and myocardial salvage. Thus, the initial size of the area at risk is an important determinant of the effectiveness of various treatments in reducing infarct size.

978 Usefulness of Defibrotide in Protecting Ischemic Myocardium from Early Reperfusion Damage
CHRISTOPH THIEMERMANN, PETRA LÖBEL, and KARSTEN SCHRÖR

Reperfusion of an occluded coronary vessel after ischemia initially leads to further tissue injury, including early reperfusion arrhythmias. Cats were subjected to 3 hours of coronary artery ligation followed by 2 hours of reperfusion. Compared with sham-operated cats, there was a considerable loss of CK-specific activity from the ischemic myocardium and electrocardiographic signs of myocardial necrosis. Treatment with defibrotide, starting at 30 minutes after coronary occlusion, largely protected from tissue damage as seen in the 60% inhibition of CK loss, inhibition of ST-segment elevations and prevention of Q-wave enlargement in the electrocardiogram. Defibrotide also antagonized ischemia-induced platelet activation and secretion, prevented fatal arrhythmias and was found to stimulate prostacyclin formation in a separate set of experiments. These data indicate beneficial cardioprotective actions of this new compound in myocardial reperfusion damage.

983 The Healing Process in Normal Canine Arteries and in Atherosclerotic Monkey Arteries After Transluminal Laser Irradiation
GEORGE S. ABELA, FILIPPO CREA, JAMES E. SEEGER, DAISEY FRANZINI, ALBERT FENECH, SIGURD J. NORMANN, ROBERT L. FELDMAN, CARL J. PEPINE, and C. RICHARD CONTI

The immediate and short-term response of normal and atherosclerotic arteries was studied in dogs and monkeys. Lasing was done via a fiber-catheter delivery system in an intact circulation. To maximize wall injury, the arteries were lased at an acute angle to the arterial wall. Evaluation of the effects using angiographic and histologic

Continued on page A34

examinations were made at 1 hour and at 2, 4, 7, 14, 30 and 60 days. The data show that lasing of the arterial wall results in discrete spots. They might occur inadvertently while attempting laser angioplasty, but they heal completely by 30 days after lasing.

989 Validation of Instantaneous Pressure Gradients Measured by Continuous-Wave Doppler in Experimentally Induced Aortic Stenosis

MARK J. CALLAHAN, A. JAMIL TAJIK, QIAN SU-FAN, and ALFRED A. BOVE

In 8 dogs, an ascending aortic snare was adjusted to produce left ventricular (LV) outflow gradients from 4 to 179 mm Hg. Pressure-tip transducer catheters recorded LV and aortic pressures simultaneously with a continuous-wave Doppler signal. In 120 randomly selected sinus beats, Doppler-derived maximal gradient correlated well with maximal instantaneous catheter gradient ($r = 0.99$). Mean gradients were also closely related. For gradients greater than 100 mm Hg, the correlation remained good ($r = 0.98$), but for gradients less than 50 mm Hg, the correlation was not as precise ($r = 0.81$). No correlation was observed between the timing of maximal Doppler velocity and either maximal or mean catheter gradient. All 120 cycles were digitized at 10-m/s intervals throughout systole. For the 2,742 pairs of points so obtained, the correlation was excellent ($r = 0.95$). These results provide further validation of the use of continuous-wave Doppler in the assessment of maximal mean and instantaneous gradients.

BRIEF REPORTS

994 Dynamic Nature of Coronary Collateral Blood Flow

DAVID S. KRAMER, and JOHN MICHAEL CRILEY

995 Pacemaker Malfunction After Nitrous Oxide Anesthesia

GERVASIO A. LAMAS, GEORGE S. REBECCA, NINA S. BRAUNWALD, and ELLIOTT M. ANTMAN

996 Angiographic Diagnosis of Coronary Sinus Ostium Atresia

SCOTT B. YEAGER, ARPY A. BALIAN, ROBERT A. GUSTAFSON, and WILLIAM A. NEAL

997 Contrast-Enhanced Cine Computed Tomography for Diagnosis of Right Coronary Artery to Coronary Sinus Arteriovenous Fistula

ROBERT M. MacMILLAN, ALI SHAHRIARI, SUMITHISENA, BARBARA K. FENDER, VLADIR MARANHAO, and DONALD CLARK

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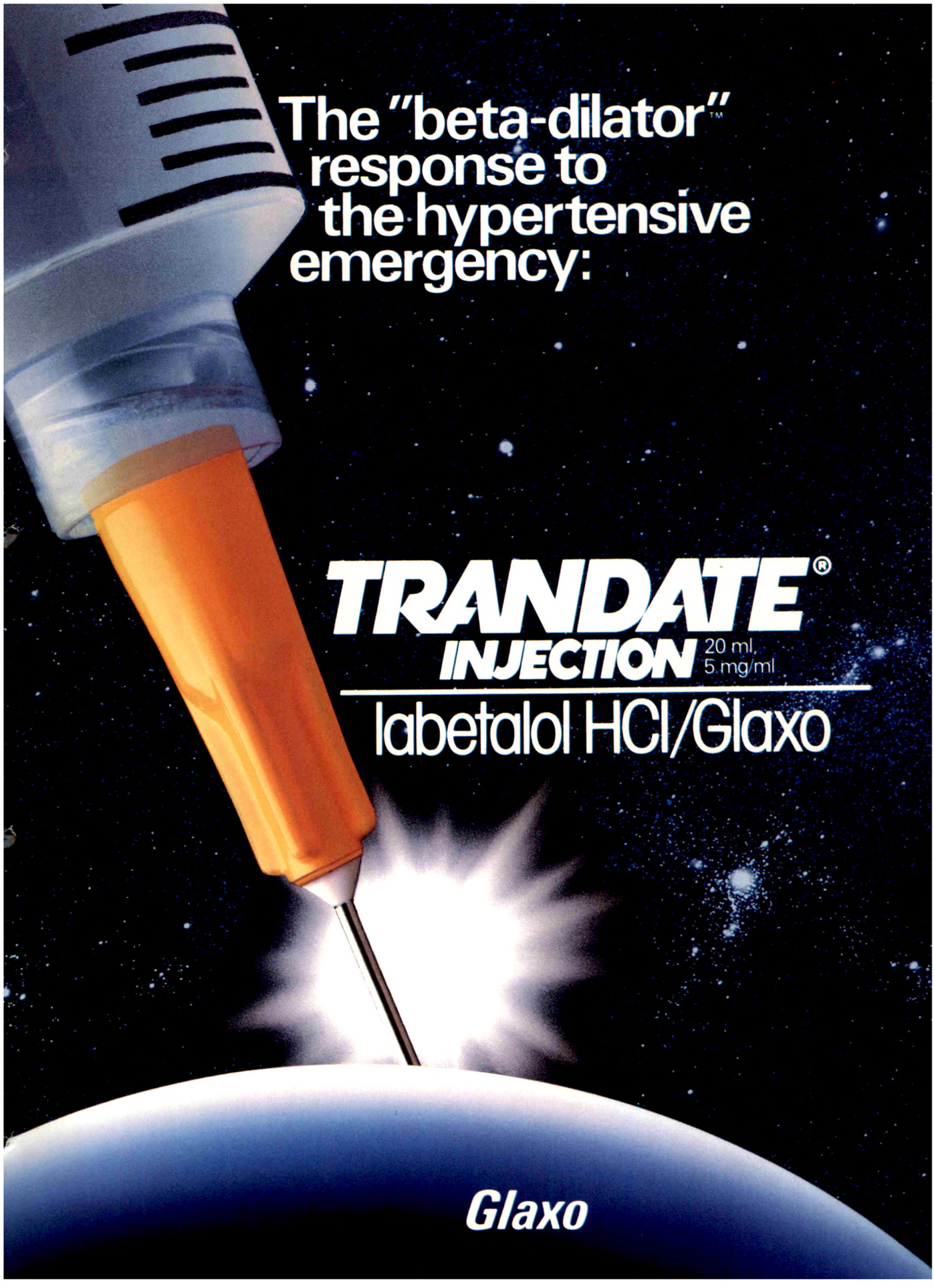
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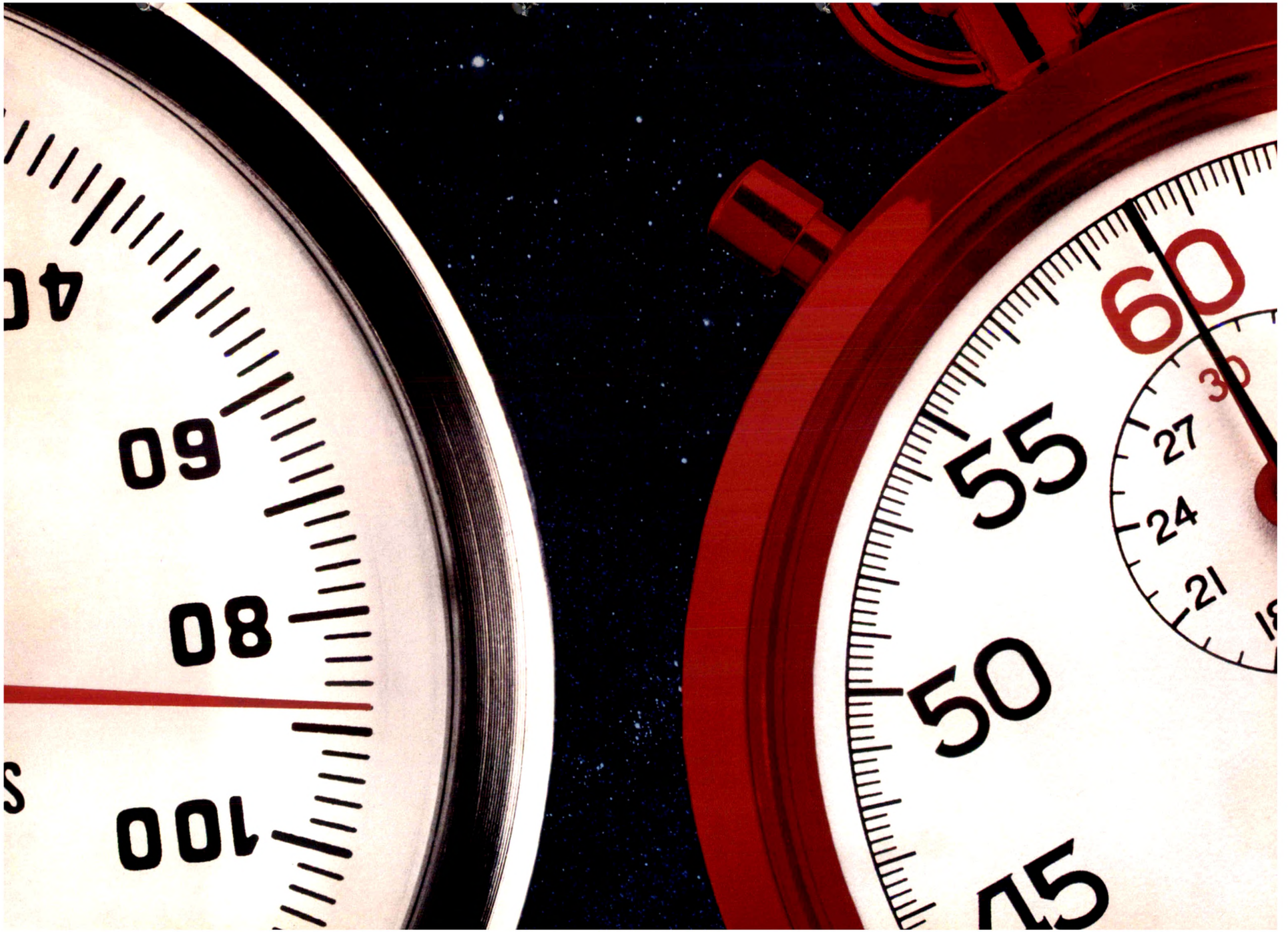
TRANDATE®
INJECTION 20 ml, 5 mg/ml
labetalol HCl/Glaxo
Glaxo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For hypertensive emergency

TRANDATE® INJECTION 20 ml, 5 mg/ml

labetalol HCl/Glaxo

The "beta-dilator"™ response: control within minutes

Action within a minute. Trandate® (labetalol HCl/Glaxo) Injection rapidly, predictably lowers blood pressure by lowering total peripheral resistance (TPR), while maintaining cardiac output.[1,2] The "beta-dilator"™ effect of simultaneous beta blockade and alpha blockade-induced vasodilation is apparent within a minute.

Rapid control. Full effect of an IV dose is apparent in 5 to 10 minutes: helps avoid hypotensive "overshoot," facilitates monitoring.

Cost control. Rapid effect may shorten hospital stay and beneficially affect costs under DRG's.

Well tolerated.* The most commonly reported adverse reactions: postural hypotension,† dizziness,† paresthesias, increased sweating and nausea.

Smooth transition to oral therapy with the same agent. Control of hypertensive crisis with Trandate Injection allows continued control on oral therapy with no need to change agents.

Trandate Injection—the "beta-dilator"™ response to hypertensive emergencies...another original product of Glaxo research.

* Patients should always be kept in a supine position during IV drug administration. See **DOSAGE AND ADMINISTRATION** section of Prescribing Information before initiating therapy.

† The episodes of postural hypotension and dizziness occurred primarily in one study in which patients were placed in an upright position within three hours of dosing for evaluation.

For a discussion of **ADVERSE REACTIONS**, please see Brief Summary of Prescribing Information on the last page of this advertisement.

Glaxo

For hypertensive emergency

TRANDATE® INJECTION 20 ml, 5 mg/ml

labetalol HCl/Glaxo

The "beta-dilator"™ response: control within minutes

- Trandate Injection can be administered as repeated IV injections, or by continuous infusion
- After initial dosing, further blood pressure reductions can be achieved with additional injections or by slow continuous infusion
- Discontinue Trandate Injection when blood pressure goal is achieved—when supine blood pressure has begun to rise, oral therapy may be initiated
- Patients should be kept in the supine position during IV drug administration. See **DOSAGE AND ADMINISTRATION** section of Prescribing Information before initiating therapy

For a discussion of **ADVERSE REACTIONS**, please see Brief Summary of Prescribing Information on the last page of this advertisement.

References: 1. Wallin JD, O'Neill WM Jr: Labetalol, current research and therapeutic status. *Arch Intern Med* 1983; 143:485-490. **2.** MacCarthy EP, Bloomfield S: Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. *Pharmacotherapy* 1983;3(4):193-219.

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March 1985

TRANDATE® Injection
(labetalol hydrochloride)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: TRANDATE® (labetalol HCl) Injection is indicated for control of blood pressure in severe hypertension.

CONTRAINDICATIONS: TRANDATE® Injection is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitilization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Ischemic Heart Disease: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TRANDATE is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.

Nonallergic Bronchospasm (eg, chronic bronchitis and emphysema): Since TRANDATE Injection at the usual intravenous therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.

Pheochromocytoma: Intravenous labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

Rapid Decreases of Blood Pressure: Caution must be observed when reducing severely elevated blood pressure. Although such findings have not been reported with intravenous labetalol HCl, a number of adverse reactions, including cerebral infarction, optic nerve infarction, angina and ischemic changes in the electrocardiogram, have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as 1 or 2 days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

PRECAUTIONS: General: ***Impaired hepatic function*** may diminish metabolism of TRANDATE® Injection.

Hypotension: Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

Jaundice or Hepatic Dysfunction: On rare occasions, oral labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) TRANDATE Injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.

When the patient is started on TRANDATE Tablets, following adequate control of blood pressure with TRANDATE Injection, appropriate directions for titration of dosage should be provided (see **DOSAGE AND ADMINISTRATION**).

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted: While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: Routine laboratory tests are ordinarily not required before or after intravenous labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: Since TRANDATE (labetalol HCl) Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C: Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the MRHD, respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE® (labetalol HCl) Injection is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: TRANDATE® Injection is usually well tolerated. Most adverse effects have been mild and transient and, in controlled trials involving 92 patients, did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with TRANDATE Injection with the incidence per 100 patients as noted:

Cardiovascular System: Ventricular arrhythmia in 1.

Central and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/skin in 7; hypoesthesia (numbness) and vertigo in 1 each.

Gastrointestinal System: Nausea in 13; vomiting in 4; dyspepsia and taste distortion in 1 each.

Metabolic Disorders: Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.

Psychiatric Disorders: Somnolence/yawning in 3.

Respiratory System: Wheezing in 1.

Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see TRANDATE Tablet Product Information for details.) Certain of the side effects increased with increasing oral dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are probably or possibly dose-related.

Labetalol HCl Daily Dose (mg)	**200**	**300**	**400**	**600**	**800**	**900**	**1200**	**1600**	**2400**
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	2	3	3	3	5	1	9	13	16
Fatigue	2	1	4	4	5	3	7	6	10
Nausea	<1	0	1	2	4	0	7	11	19
Vomiting	0	0	<1	<1	<1	0	1	2	3
Dyspepsia	1	0	2	1	1	0	2	2	4
Paresthesias	2	0	2	2	1	1	2	5	5
Nasal Stuffiness	1	1	2	2	2	2	4	5	6
Ejaculation Failure	0	2	1	2	3	0	4	3	5
Impotence	1	1	1	1	2	4	3	4	3
Edema	1	0	1	1	1	0	1	2	2

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl during investigational use and extensive foreign marketing experience.

Clinical Laboratory Tests: Among patients dosed with TRANDATE Tablets, there have been reversible increases of serum transaminases in 4% of patients tested and, more rarely, reversible increases in blood urea.

OVERDOSAGE: Overdosage with TRANDATE® Injection causes excessive hypotension which is posture sensitive and, sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: **Excessive bradycardia**—administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac failure**—administer a digitalis glycoside and a diuretic. **Hypotension**—administer vasopressors, eg, norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. **Bronchospasm**—administer a $beta_2$-stimulating agent and/or a theophylline preparation.

If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION: Initiation of Dosing with TRANDATE Tablets: Subsequent oral dosing with TRANDATE Tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 mg or 400 mg, depending on the blood pressure response. Thereafter, **inpatient titration with TRANDATE Tablets may proceed as follows:**

Inpatient Titration Instructions

Regimen	Daily Dose*
200 mg bid	400 mg
400 mg bid	800 mg
800 mg bid	1600 mg
1200 mg bid	2400 mg

*If needed, the total daily dose may be given in three divided doses.

While in the hospital, the dosage of TRANDATE (labetalol HCl) Tablets may be increased at one-day intervals to achieve the desired blood pressure reduction.

For subsequent outpatient titration or maintenance dosing see TRANDATE Tablets Product Information **DOSAGE AND ADMINISTRATION** for additional recommendations.

HOW SUPPLIED: TRANDATE® Injection, 5 mg/ml, is supplied in 20 ml (100 mg) ampules, box of 1 (NDC 0173-0350-59).

Store between 2° and 30° C (36° and 86° F.) Do not freeze.

Manufactured for Glaxo Inc. Research Triangle Park, NC 27709
by Schering Pharmaceutical Corporation (PR), Manati, PR 00701
October 1984

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Glaxo

Glaxo, Inc., Research Triangle Park, NC 27709

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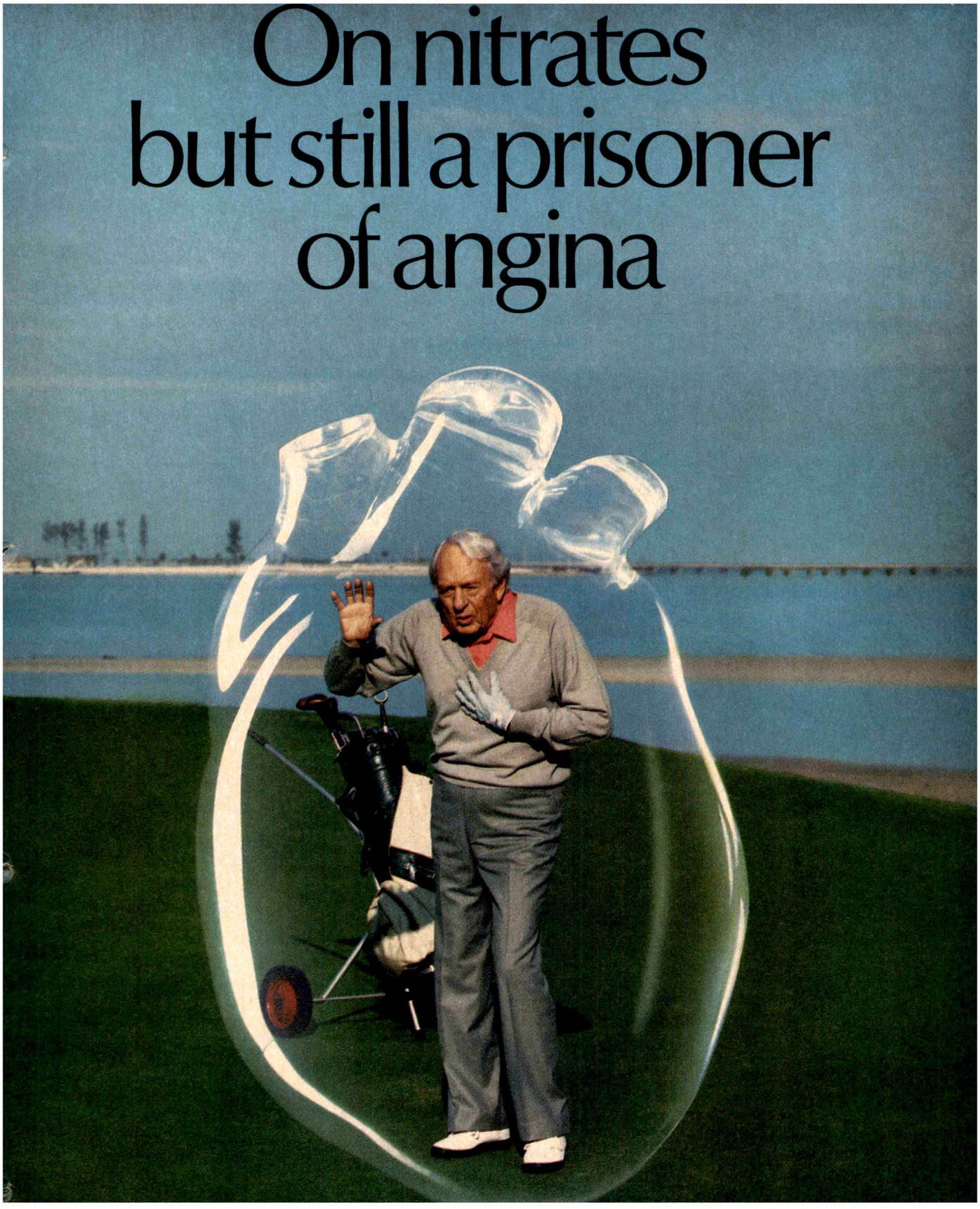
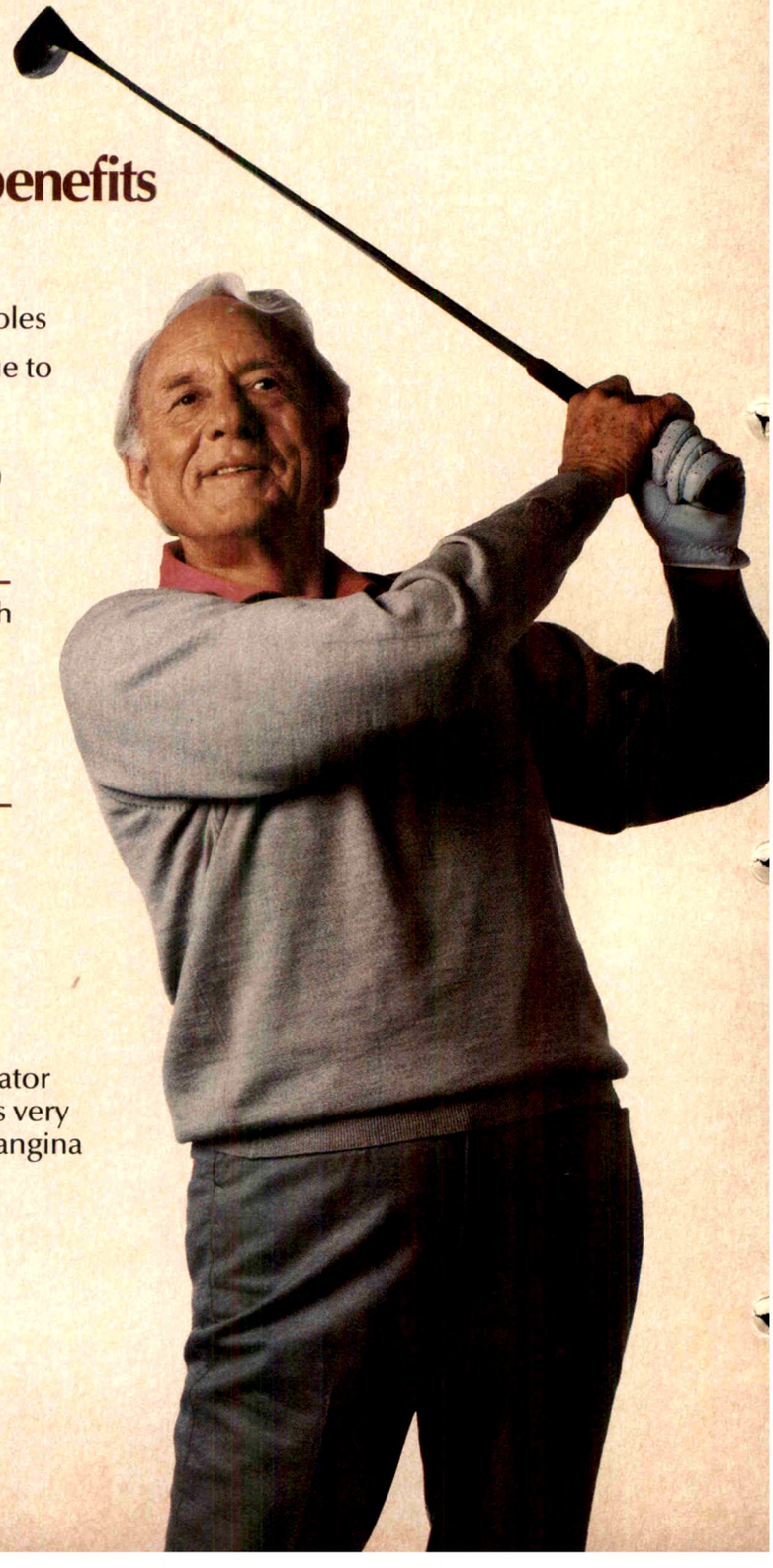
On nitrates but still a prisoner of angina



When nitrates alone are not enough

Add **Calan®** *TABLETS*
80 mg and 120 mg
(verapamil HCl)



Calan plus nitrates: Unique hemodynamic benefits

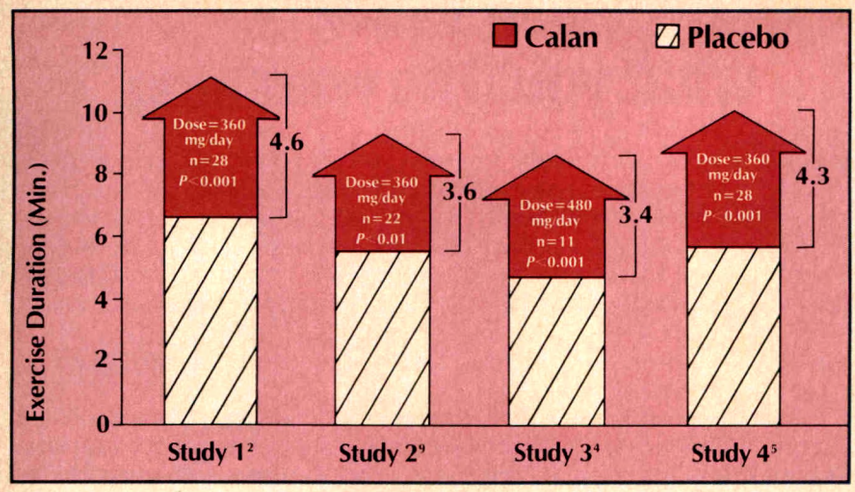
- increased myocardial oxygen supply—prevents vasoconstriction both in large coronary arteries and in coronary arterioles
- reduced myocardial oxygen demand due to
  - —a reduction in peripheral vascular resistance (afterload)
  - —a decrease in venous return (preload)
  - —a modest decrease in contractility

"It makes sense to treat those patients [with chronic stable angina]... [with] an agent that has a beneficial effect on both oxygen demand and supply, rather than a beta blocker which attacks just one side of that ratio."[1]

Calan plus nitrates: Efficacy for all types of angina

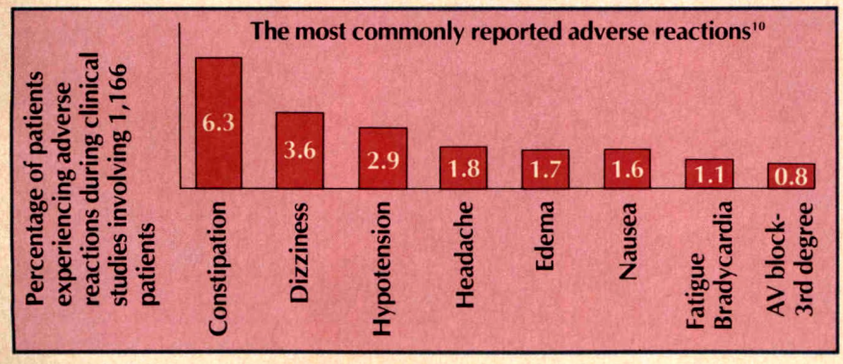
"...a combination of rate-lowering vasodilator (verapamil...) and long-acting nitrates... is very efficacious in patients with variant angina, angina of effort, and unstable angina at rest."[1]

Calan efficacy: Significant improvement in exercise tolerance[2-9]



- clinically significant improvement in exercise tolerance
- clinically significant reduction in the number of attacks and the need for sublingual nitroglycerin

Calan safety: Favorable side-effects profile



With Calan, side effects such as fatigue, mental depression, impotence or bradycardia (heart rate less than 50 beats/min) seldom occur.

In one study involving 63 patients "verapamil therapy was not discontinued in any patient because of the development of adverse reactions."[8]

Calan® *TABLETS*
80 mg and 120 mg
(verapamil HCl)

References:

1. Hillis, D., in Hillis, D. (Moderator); Frishman, W.; Leon, M.; Packer, M.; Robertson, R. M.; Subramanian, B., and Winniford, M. (Discussants): The Expanding Role of Calcium Channel Blockers, 1984. **2.** Subramanian, B., and others: Long-Term Antianginal Action of Verapamil Assessed with Quantitated Serial Treadmill Stress Testing, Am. J. Cardiol. *48*: 529-535 (Sept.) 1981. **3.** Subramanian, B.: Long-Term Therapy of Angina with Calcium Antagonists, Cardiovasc. Rev. Rep. *4*:493-497 (April) 1983. **4.** Leon, M.B.: Combination Therapy Using Calcium-Channel Blockers and Beta Blockers in Patients with Chronic Stable Angina Pectoris, Cardiovasc. Rev. Rep. *4*:171-177 (Feb.) 1983. **5.** Subramanian, V. B., and others: Rationale for the Choice of Calcium Antagonists in Chronic Stable Angina: An Objective Double-Blind Placebo-Controlled Comparison of Nifedipine and Verapamil, Am. J. Cardiol. *50*:1173-1179 (Nov.) 1982. **6.** Weiner, D. A., and others: Efficacy and Safety of Verapamil in Patients With Angina Pectoris After 1 Year of Continuous, High-Dose Therapy, Am. J. Cardiol. *51*:1251-1255 (May 1) 1983. **7.** Frishman, W. H., and others: Superiority of Verapamil to Propranolol in Stable Angina Pectoris: A Double-blind, Randomized Crossover Trial, Circulation *65* (Suppl. 1):51-59 (Jan.) 1982. **8.** Scheidt, S., and others: Long-Term Effectiveness of Verapamil in Stable and Unstable Angina Pectoris: One-Year Follow-Up of Patients Treated in Placebo-Controlled Double-Blind Randomized Clinical Trials, Am. J. Cardiol. *50*:1185-1190 (Nov.) 1982. **9.** Bowles, M. J., and others: Double-blind Randomized Crossover Trial of Verapamil and Propranolol in Chronic Stable Angina, Am. Heart J. *106*:1297-1306 (Dec.) 1983. **10.** Product Labeling.

SEARLE

Please see following page for a brief summary of the complete prescribing information.

5W001T

Calan® **TABLETS**
80 mg and 120 mg
(verapamil HCl)

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block.
Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension, usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Elevations of liver enzymes have been reported. Four cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Patients with atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) may develop a very rapid ventricular response after receiving verapamil (or digitalis). Treatment is usually DC-cardioversion. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.
Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.
Adverse Reactions: Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in less than 0.5% of patients, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions, spotty menstruation, ecchymosis, bruising, gynecomastia, and psychotic symptoms. Overall continuation rate was 94.5% in 1,166 patients.

5/85 • 5W021V2

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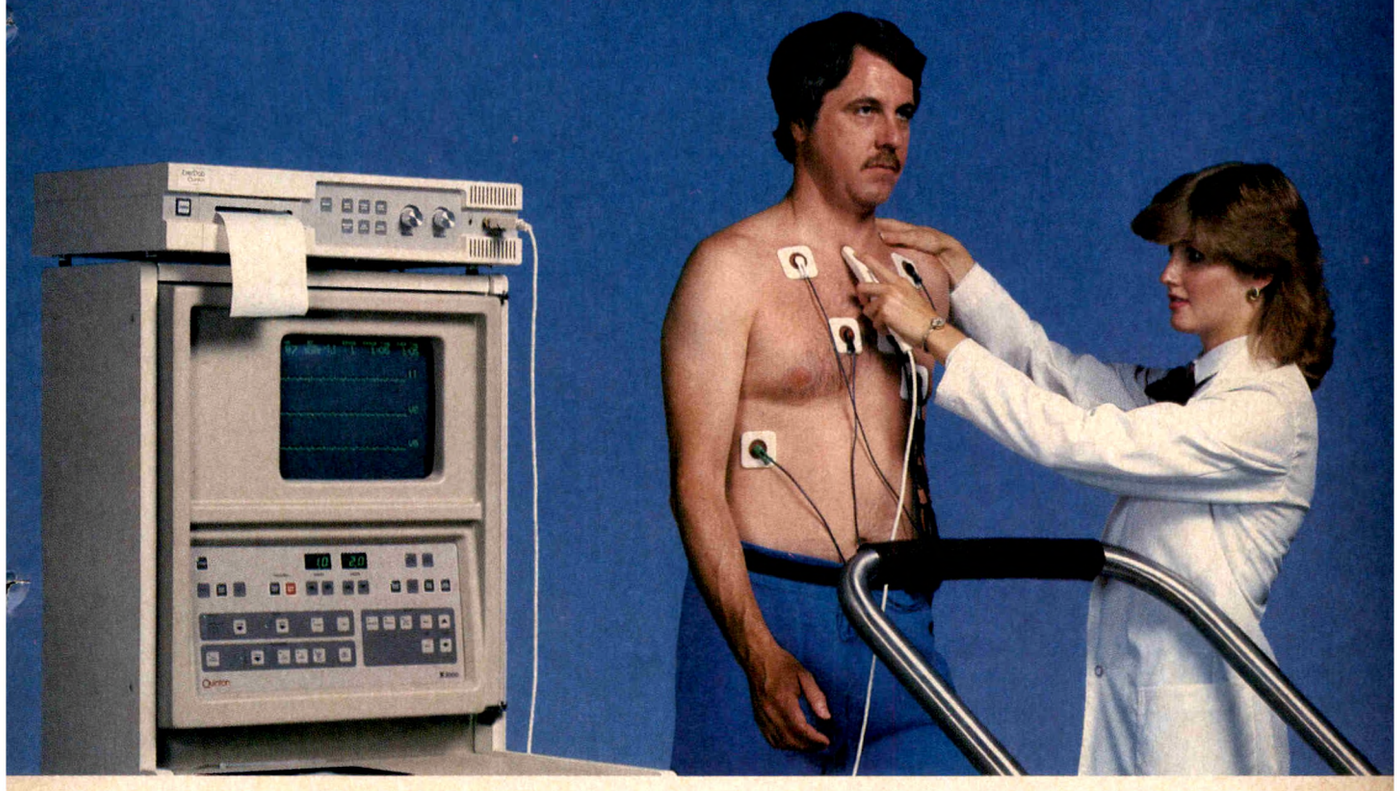
The American Journal of Cardiology

Introducing a Noninvasive Method for Assessing Left Ventricular Function



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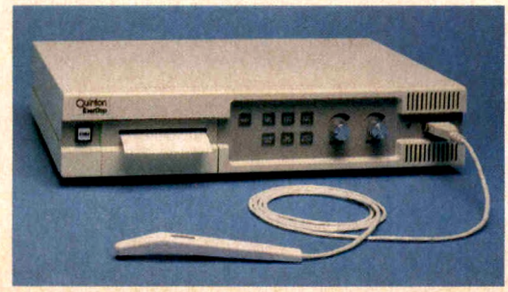

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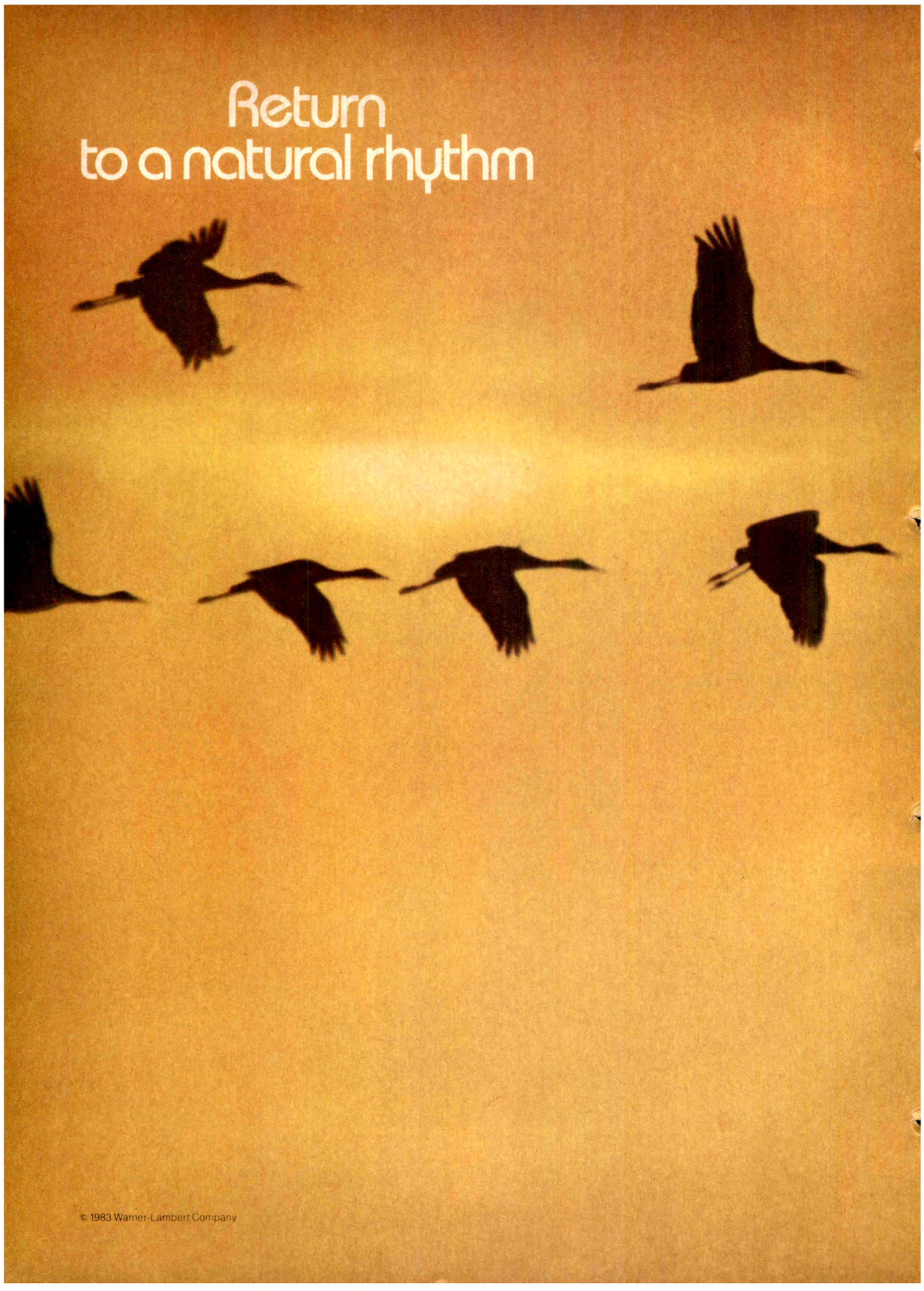

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Return to a natural cardiac rhythm

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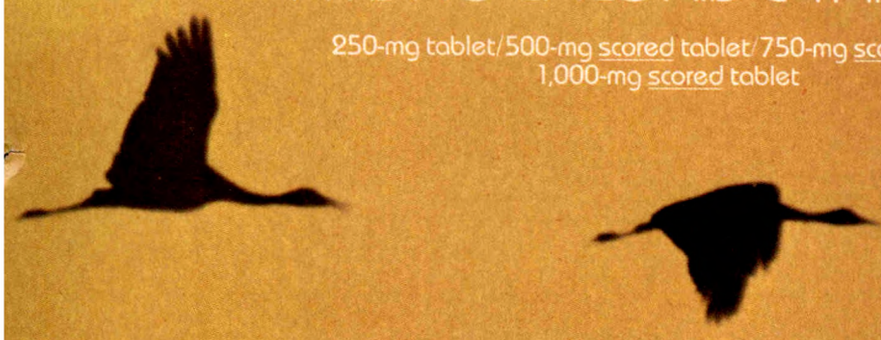

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Please see next page for brief summary of prescribing information.

PROCAN® SR (procainamide hydrochloride tablets)
SUSTAINED RELEASE
Before prescribing, please see full prescribing information.
A Brief Summary follows.

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions, ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: Hypersensitivity to procainamide is an absolute contraindication. In this connection, cross-sensitivity to procaine and related drugs must be borne in mind.

Procainamide should not be administered to patients with complete atrioventricular heart block. It is also contraindicated in cases of second degree and third degree A-V nodal block unless an electrical pacemaker is operative.

It has been suggested that procainamide be contraindicated in patients with myasthenia gravis.

WARNINGS: Granulocytopenia may follow the use of procainamide, and deaths from sepsis have occurred. Leukocyte changes are most likely to occur during the first three months of therapy. During this time routine blood counts should be done at least every two weeks, and thereafter at longer intervals throughout maintenance procainamide therapy. Complaints of malaise and aches (a flu-type syndrome) are often reported in association with the granulocyte depression.

Patients should be instructed to report such symptoms promptly, as well as any soreness of mouth, throat or gums, unexplained fever, or symptoms of an upper respiratory tract infection. If these should occur and a complete blood count indicates a granulocyte depression, procainamide therapy should be discontinued immediately and appropriate treatment instituted. Recovery of leukocyte count usually occurs within a few weeks.

The incidence of granulocytopenia appears to be higher with procainamide sustained-release tablets than with standard tablets.

PRECAUTIONS: General—During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Serious hypotension can result from peripheral vasodilation and from decreases in cardiac output. At high plasma levels, procainamide may produce sinus tachycardia due to reflex sympathetic response to its hypotensive effect. Large doses may increase cardiac automaticity and can induce complete atrioventricular block, cardiac standstill, or ventricular extrasystoles that may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram: a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged, and the QRS and T waves show some decrease in voltage.

Antinuclear antibodies (ANA) are often found in patients receiving long-term procainamide therapy. The induction of ANA appears to be independent of dosage. Patients with procainamide-induced increases in ANA titers may develop a syndrome resembling systemic lupus erythematosus (SLE). The mechanism of this syndrome is uncertain. Polyarthralgia, arthritic symptoms, and pleuritic pain are common symptoms; to a lesser extent fever, myalgia, skin lesions, pleural effusion, pericarditis, headache, fatigue, weakness, nausea and abdominal pain may occur. Rare cases of thrombocytopenia, Coombs' positive hemolytic anemia, increased SGOT, SGPT, and serum amylase have been reported which may be related to this SLE-like syndrome.

It is recommended that tests for systemic lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy. The drug should be discontinued if there is a rising ANA titer or clinical symptoms of SLE appear. The SLE-like syndrome may be reversible upon discontinuation of the drug. If discontinuation does not cause remission of the symptoms, corticosteroid therapy may be effective. If the SLE-like syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, corticosteroid suppressive therapy may be used concomitantly with procainamide.

Information for Patient—Practitioners should give the following information and instructions to patients receiving Procan SR.

1. Do not crush or chew these tablets. Swallow them whole.
2. Take this medicine exactly as directed by your doctor. Do not miss any doses and do not take more medicine than ordered. Do not stop taking this medicine without first checking with your doctor.
3. If you miss a dose and remember within one hour or so, take it as soon as possible. Then go back to your regular dosing schedule. Do not take double doses. If you have any questions about this, check with your doctor.
4. Report to your doctor any flu-type symptoms, such as malaise and aches, as well as any soreness of the mouth, throat or gums, unexplained fever, skin rash, unusual bleeding or bruising, symptoms that resemble arthritis, or symptoms of an upper respiratory tract infection.
5. Do not be concerned if you occasionally notice in your stool something that looks like a tablet. In Procan SR (procainamide hydrochloride tablets), the drug is 'held' in a wax core that has been specially designed to slowly release the drug for your body to absorb. When this process is completed the empty, nonabsorbable wax core, which looks nearly unchanged, is eliminated from your body.
6. Keep container tightly closed and store in a cool, dry place.

Laboratory Tests—Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals.

Routine blood counts are advisable during maintenance procainamide therapy. See WARNINGS for additional information.

Plasma concentrations of procainamide and NAPA should be monitored in patients with renal disease, hepatic disease, cardiac failure, or low cardiac output states.

Drug Interactions

1. **Antiarrhythmics:** Concurrent use with procainamide may result in additive cardiac effects and/or additive toxic effects.
2. **Anticholinergics:** Procainamide enhances the anticholinergic effects. Extreme caution must be exercised with such a combination.
3. **Anticholinesterases:** Procainamide antagonizes the effect of anticholinesterases in myasthenia gravis, and paralysis returns.
4. **Antihypertensives:** Procainamide may potentiate the hypotensive effects of thiazide diuretics and other antihypertensive agents. Adjustment of dosage may be required.
5. **Cimetidine:** It has been reported that the histamine H_2-antagonist cimetidine reduces renal clearance of procainamide and NAPA, resulting in higher plasma concentrations for longer durations. Caution should be exercised when administering these drugs concurrently, especially in the elderly, who have a reduced ability to clear all three. Dosage modification may be required.
6. **Neuromuscular Blocking Agents:** Procainamide potentiates the effects of skeletal muscle relaxants such as succinylcholine. It also may enhance or prolong the neuromuscular blocking activity of bacitracin, colistimethate, dihydrostreptomycin, gentamicin, gramicidin, kanamycin, neomycin, polymyxin B, streptomycin, and viomycin, producing respiratory depression.

Pregnancy—Pregnancy Category C. Animal reproduction studies have not been conducted with procainamide. It is also not known whether procainamide can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Procainamide should be given to a pregnant woman only if clearly needed.

Nursing Mothers—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when procainamide is administered to a nursing woman.

ADVERSE REACTIONS: Most frequent, especially with large oral doses:
1. Anorexia 2. Nausea 3. Vomiting 4. Diarrhea 5. Urticaria 6. Pruritus.

Less frequent: 1. Reactions in patients on long-term procainamide therapy: a. Antinuclear antibodies (ANA) b. Syndrome resembling systemic lupus erythematosus (SLE) (See PRECAUTIONS).

2. Hypersensitivity reactions: a. Angioneurotic edema b. Maculopapular rash c. Fever d. Eosinophilia e. Hypergammaglobulinemia.

Infrequent: 1. Granulocytopenia, sometimes resulting in death (See WARNINGS) 2. Convulsions 3. Psychosis with hallucinations 4. Confusion 5. Mental depression 6. Giddiness 7. Lightheadedness 8. Weakness 9. Bitter taste.

Rare: 1. Hypotension 2. A case was reported with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following a single dose of the drug.

OVERDOSAGE: Signs and symptoms of overdosage of procainamide include severe hypotension, ventricular fibrillation, widening of the QRS complex, junctional tachycardia, intraventricular conduction delay, oliguria, lethargy, confusion, nausea, and vomiting.

If ingestion is recent, gastric lavage or emesis may reduce absorption. Dopamine, phenylephrine or levarterenol may be helpful in reversing severe hypotensive responses.

Management of overdosage includes symptomatic treatment with ECG and blood pressure monitoring. Procainamide toxicity can usually be treated, if necessary, by administering vasopressors after adequate fluid volume replacement. Intravenous infusion of 1/6 molar sodium lactate injection reportedly reduces the cardiotoxic effects of procainamide.

The urinary elimination of procainamide is proportional to the glomerular filtration rate but is also affected by changes in urinary pH. Procainamide is relatively lipid-soluble as a free base, but the ionized form is not. Acid urine, therefore, leads to ion trapping of procainamide which enters the urine by passive diffusion from the plasma. Accordingly, renal clearance of procainamide can be considerably increased by maintaining a low urinary pH and high flow rates.

If procainamide toxicity causes severe hypotension and renal insufficiency, urinary elimination of procainamide and NAPA is decreased, and hemodialysis may be required. Hemodialysis significantly reduces the serum half-life of procainamide, and effectively removes procainamide and NAPA. Peritoneal dialysis is not effective.

It has been reported that one patient who ingested approximately 7 grams of procainamide hydrochloride recovered after treatment consisting of IV levarterenol, IV furosemide, attempted volume expansion with albumin, and hemodialysis. Also reported is the case of an elderly patient who recovered after ingestion of approximately 19 grams of procainamide hydrochloride. The patient was treated with IV isoproterenol and IV epinephrine. The latter report suggested that insertion of a ventricular pacing electrode is a reasonable precautionary measure in case high grade A-V block develops.

Storage Conditions—Protect from moisture. Store bottles below 30° C (86° F). Store unit-dose packages at controlled room temperature, 15°-30° C (59°-86° F). 0207G012
Caution: Federal law prohibits dispensing without prescription.

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PD-59-JA-1334-P-4(8-85)

DECEMBER 1, 1985

The American Journal of CARDIOLOGY®

VOLUME 56

NUMBER 15

SYSTEMIC HYPERTENSION

Systolic Hypertension in the Elderly Program (SHEP): Antihypertensive Efficacy of Chlorthalidone

STEPHEN B. HULLEY, MD, MPH, CURT D. FURBERG, MD, BARRY GURLAND, MD, ROBERT McDONALD, MD, H. MITCHELL PERRY, MD, HAROLD W. SCHNAPER, MD, JAMES A. SCHOENBERGER, MD, W. McFATE SMITH, MD, MPH, and THOMAS M. VOGT, MD, MPH, *for the* SHEP Research Group

The Systolic Hypertension in the Elderly Program (SHEP) is a randomized, blinded test of the efficacy of antihypertensive drug treatment. In a large feasibility trial, 551 men and women who had isolated systolic hypertension and were at least 60 years old received chlorthalidone (25 to 50 mg/day) or matching placebo as the step I drug. After 1 year, 83% of the chlorthalidone group and 80% of the placebo group were still taking SHEP medications. Of those still taking chlorthalidone, 88% had reached goal blood pressure (BP) without requiring a step II drug, and most had responded to the lower dose (25 mg/day). The BP response was similar in all age, sex and race subgroups, with an overall mean difference between randomized groups of 17 mm Hg for systolic BP ($p < 0.001$) and 6 mm Hg for diastolic BP ($p < 0.001$). The only common adverse effects were asymptomatic changes in the serum levels of potassium (0.5 mEq/liter lower in the chlorthalidone group, $p < 0.001$), uric acid (0.9 mg/dl higher, $p < 0.001$) and creatinine (0.08 mg/dl higher, $p = 0.02$). This study indicates that chlorthalidone is effective for lowering BP in elderly patients with systolic hypertension and sets the stage for a larger trial of the effects of such treatment on the incidence of cardiovascular disease.

(Am J Cardiol 1985;56:913–920)

From the Departments of Epidemiology and International Health and Medicine, and the Institute for Health Policy Studies, University of California, San Francisco, California; National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; Center for Geriatrics and Gerontology and Long-Term Care Gerontology Center, Columbia University and New York State Office of Mental Health, New York, New York; School of Medicine and Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; Hypertension Division, Department of Internal Medicine, Washington University, St. Louis, Missouri; Division of Gerontology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama; Department of Preventive Medicine, Rush–Presbyterian–St. Lukes Medical Center, Chicago, Illinois; and Kaiser Foundation Hospitals, Center for Health Research, Portland, Oregon. This study was supported by grants HL23914, HL23913, HL23924, HL23916, HL23917 and HL23919 from the National Heart, Lung, and Blood Institute, the National Institute of Aging and the National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland. Manuscript received February 27, 1985; revised manuscript received June 4, 1985, accepted June 6, 1985.

Address for reprints: Stephen B. Hulley, MD, Building One, Room 201, San Francisco General Hospital, San Francisco, California 94110.

The 1984 report from the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure[1] provided a comprehensive set of policy guidelines on the management of diastolic hypertension. One important issue that remains unsettled, however, is whether to treat isolated systolic hypertension.[1–3] The prevalence of this condition, defined as a systolic blood pressure (BP) of 160 mm Hg or greater with a diastolic BP less than 90 mm Hg, increases to about 20% in both sexes by age 80 years[4–6]; 3 million persons in the U.S. are affected. The health implications of isolated systolic hypertension are similar to those for diastolic hypertension: a 2- to 3-fold excess risk of cardiovascular mortality.[5,7–10] Whether antihypertensive treatment with drugs will prevent some or

all of the excess cardiovascular events and whether such treatment is safe remain to be established.

The Systolic Hypertension in the Elderly Program (SHEP) is a large collaborative trial to resolve these uncertainties in a randomized design with a blinded placebo control. Findings pertaining to 3 of the topics studied during the 4-year feasibility study are presented: (1) the degree to which elderly patients comply with the antihypertensive treatment protocol, (2) the degree to which their systolic BP responds to drug therapy, and (3) the degree to which adverse effects are a problem.

Methods

Overall design: Elderly men and women who met eligibility criteria at 4 baseline examinations were randomized in a double-blind fashion to chlorthalidone or matching placebo. Those who did not respond adequately to 1 capsule daily of this step I drug (25 mg of chlorthalidone) progressed sequentially to 2 capsules daily and to step II drugs or placebo. The outcome variables were the compliance with the treatment protocol, the BP response and the adverse effects of medication.

Recruitment: The recruitment of study participants in the 5 clinical centers has been described in detail[11–14] and is summarized briefly herein. A total of 27,199 men and women aged 60 or older volunteered to have 3 BP measurements during screening examinations carried out in various community sites;[14] 16,629 (61%) reported that they were not receiving antihypertensive medication and 2,601 (16%) of these met the BP criteria for attending the first baseline clinic visit (systolic BP 160 to 239 mm Hg and diastolic BP less than 100 mm Hg). Of these 1,834 (71%) attended this first visit. A surprisingly large proportion of those screened (39%) reported current use of antihypertensive drugs; 1,899 of these were invited and 696 agreed to a carefully supervised withdrawal of medications. Of these, 308 became eligible for the first clinic visit and 125 were randomized.

Three baseline clinic visits were used to identify the participants who were subsequently randomized into the study. In addition to the BP criteria at each of these visits (systolic BP 150 to 239 mm Hg and diastolic BP less than 95 mm Hg at each of the first 2 clinic visits; systolic BP 160 to 219 mm Hg and diastolic BP less than 90 mm Hg at the third clinic visit), eligibility requirements included geographic stability and absence of the following: coronary bypass surgery within 2 years or heart attack within 6 months; stroke with residua; current treatment with antihypertensive drugs, insulin or anticoagulants; allergy to study medications; specified arrhythmias or a pacemaker; uncontrolled congestive heart failure; serum creatinine level of 2.0 mg/dl or more; alcohol abuse; cancer or other life-threatening disease; chronic obstructive pulmonary disease; peripheral vascular disease with tissue injury; senile dementia; residence in a nursing home; carotid bruit with history of transient ischemic attacks; and history of malignant hypertension. Of the 2,130 participants seen at the first clinic visit, 551 (26%) reached the third clinic visit and were randomized, 422 (20%) were eligible but refused participation, 967 (45%) failed BP criteria (almost always because systolic BP was not high enough), 116 (5%) failed other explicit eligibility criteria and 74 (4%) were excluded by clinical judgment. Overall yield from screening to randomization was 2%.

Hypothesis, sample size and randomization: The written a priori hypothesis stated that participants in the step I active drug treatment group would have a lower mean systolic BP than those in the step I placebo group after 1 year of follow-up. We specified an "intention to treat" rule (with study groups divided by the randomized assignment regardless of subsequent crossovers) and a plan for replacing any missing annual visit BP with the last available value. The designated sample size of 500 had a power of 0.90 to detect a mean difference in systolic BP of 6 mm Hg at a 1-tailed α of 0.05.

Each randomization was carried out by telephone between the clinic staff and the coordinating center data manager, who checked that eligibility criteria were met before assigning the participant to chlorthalidone or placebo. The ratio of assignment to these 2 groups was 4:1 to increase the number of participants who would receive an active step II drug and the power for contrasts among them. We used an adaptive randomization procedure that varied treatment assignment probabilities by 10% in one or the other direction in order to balance the step I study groups within race, sex, age and baseline systolic BP strata.[15]

Blood pressure treatment: Upon randomization into the study, participants entered the step-up protocol and received 25 mg/day of chlorthalidone or placebo (supplied as identical capsules by USV Pharmaceutical Corp.). Clinic visits were then scheduled at 4-week intervals unless the participants achieved goal BP (systolic BP less than 160 mmHg or 20 mm Hg below the baseline level, whichever was lower) for 2 consecutive visits, after which "maintenance" visits were scheduled at 8-week intervals. If BP had not reached goal after 4 weeks and if no adverse effects had occurred, the dosage was increased to 2 capsules of chlorthalidone or placebo daily. Twelve weeks after randomization, participants receiving chlorthalidone who had not reached goal BP were randomized to 1 of 4 step II drugs (reserpine, 0.05 mg twice daily; metoprolol, 50 mg twice daily; hydralazine, 25 mg twice daily; or matching placebo twice daily) (supplied by Ciba-Geigy). Participants receiving step I placebo who had not reached goal underwent a dummy randomization, and all received step II placebo twice daily. Twelve weeks later, the dosage for participants who still had not reached goal was doubled.

Participants on the maintenance schedule whose BP increased above goal for 2 consecutive visits were returned to the step-up schedule. Participants whose BP reached "escape" levels (that is, systolic BP of 220 mm Hg or higher or diastolic BP 100 mm Hg or higher at any visit) were seen at weekly intervals and stepped-care medications were advanced at an accelerated schedule until the BP fell below these levels or the participant reached step II, dose 2 and SHEP medications were discontinued in favor of open treatment with known drugs.

Outcome variables: *Blood pressure* was measured with a random 0 mercury manometer after participants had been sitting in a quiet room for 5 minutes. Systolic BP was defined as the first point at which sounds were recognizable, and diastolic BP as the point when sounds ceased to be heard. Two measurements were made at each visit by staff trained and certified in the procedures, and the mean was used to represent that visit. BP measurements were subjected to an extensive quality control program, including periodic recertification of the technicians, site visits by the quality control coordinator and periodic inspection of the data for low precision and digit preference.

Compliance with the SHEP treatment protocol was measured by capsule count, by self-report and by urine tests for the presence of chlorthalidone, using methods that have been described.[16] We also examined the rate at which SHEP medications were terminated in each of the study groups, and assessed the participants' adherence to the regular treatment visit schedule.

TABLE I Characteristics of the Randomized Cohort at Baseline by Study Group

	Study Group		
	Chlorthalidone (n = 443)*	Placebo (n = 108)*	Significance of Difference†
Demographics			
Aged >70 years	60%	65%	
Women	63%	64%	
Non-white	18%	20%	
Married	50%	47%	
College educated	25%	23%	
Employed	13%	13%	
Habits			
Current cigarette smokers	11%	14%	
Alcohol more than twice a week	20%	16%	
Living alone	41%	45%	
Medical history			
Antihypertensive treatment in the past	46%	50%	
Myocrdial infarction in the past	5%	2%	
Stroke in the past	1%	1%	
Current angina	2%	6%	p = 0.02
Current medications			
Digitalis	2%	0%	
Nitrates	2%	2%	
Hypoglycemic agents	3%	4%	
Librium, valium	5%	5%	
Estrogen	2%	2%	
Aspirin at least 4 times/week	26%	26%	
Physical examination			
Systolic BP, mean ± SD (mm Hg)	172 ± 11	174 ± 11	
Diastolic BP, mean ± SD (mm Hg)	75 ± 9	77 ± 8	
Heart rate, mean ± SD (beats/min)	74 ± 11	76 ± 13	
Weight, mean ± SD (lbs)	159 ± 32	158 ± 30	
Abnormal fundi	34%	26%	
Carotid bruit	5%	10%	p = 0.04

* Participants were randomized at step I in a ratio of 4:1 (chlorthalidone:placebo) to increase the number who would be available for subsequent randomization to step II active drugs. In this report only the results classified by step I randomization are reported.

† Nominal p values for the contrasts between study groups were computed by χ^2 test (Fisher's exact for contrasts with an expected n of 5 or less in any 1 cell) or a 2-tailed *t* test. No adjustment for multiple comparisons was made. The p values are given only for contrasts with $p < 0.10$.

BP = blood pressure; SD = standard deviation.

Symptoms that might represent adverse effects were assessed at every clinic visit by asking participants if they had felt unwell in any way since the prior clinic visit. At the baseline visit, the 1-month visit and the annual visit, the clinician also asked whether the participant had experienced any of 22 specified symptoms. (At the intervening visits only volunteered symptoms were recorded.) The severity of each symptom was characterized by the participant as "not troublesome," "troublesome" or "intolerable;" only the latter 2 responses are presented in this report.

Serum biochemistry levels were measured at specified intervals by Bio-Science Laboratories on a Technicon SRA-2000 multichannel analyzer using the hexokinase method for glucose, an ion-specific electrode for potassium, the uricase method for uric acid and the Jaffe reaction method (with picric acid) for creatinine; serum cholesterol levels were measured with an enzymatic method on a Cotas centrifugal analyzer. Clinicians used their judgement about prescribing potassium supplements (generally Bi-K™, 15 to 30 ml/day) to participants with low potassium levels, and allopurinol or probenecid to those with high uric acid levels. A system by which study group assignment could be discovered by local clinicians in the event of emergency was used on 3 occasions.

Data management: We developed a distributed system for data processing and telecommunications for the study.[17] This system used Wang minicomputers at each center to maximize compliance with the treatment protocol and to enhance the accuracy, timeliness and completeness of the data.

Results

Characteristics of the study cohort: Of the 551 participants in the SHEP study cohort, 443 were randomized to receive chlorthalidone as the step I drug and 108 to receive placebo. Mean values for systolic BP and diastolic BP in the chlorthalidone group at baseline were 172 and 75 mm Hg, respectively. These and other baseline variables were reasonably well distributed between the 2 randomized groups (Table I), although 2 variables (angina and carotid bruit) were more common in the placebo group at a nominal (unadjusted for multiple comparisons) 2-tailed $p < 0.05$.

Compliance: At the end of the year of observation, the vital status of all 551 participants was known. Among the 540 (98%) still alive, 93% of the chlorthalidone group and 97% of the placebo group attended the annual examination (Table II). The percentage permanently discontinuing step I SHEP drugs was 17% in the chlorthalidone group and 20% in the placebo group after 1 year of follow-up; two-thirds of these terminations occurred during the first 6 months.

Among those still taking medications at the annual visit, compliance with step I SHEP medications was assessed by counting the capsules returned at each visit, by asking the participants whether they had omitted any dosages of the SHEP medications and by

TABLE II Compliance with Step I SHEP Medications After 1 Year of Follow-Up by Study Group

	Chlorthalidone		Placebo	
	Overall Compliance in Those Alive at 1 Year*	Compliance in Those Prescribed SHEP Medications and with Complete Data†	Overall Compliance in Those Alive at 1 Year*	Compliance in Those Prescribed SHEP Medications and with Complete Data†
Attended anniversary visit	93%		97%	
SHEP medications still prescribed	83%		80%	
Capsule count reveals ≥ 80% of expected consumption since prior visit	71%	88%	69%	90%
Participants report taking all capsules in past week	76%	91%	71%	89%
Urine chlorthalidone present	72%	86%	. . .	. . .

* Vital status was established for all 551 participants, and the 540 (98%) who were alive after 1 year of follow-up are the denominator for the overall compliance columns.

† The denominator for these columns exclude the participants whose SHEP medications have been terminated and also those with incomplete compliance data (2% of the chlorthalidone and 3% of the placebo group for the capsule counts, none of either group for the self-reports and 4% of the chlorthalidone group for the urine tests).

SHEP = Systolic Hypertension in the Elderly Program.

chemically testing the urine for chlorthalidone. The results indicate that more than 85% of the participants in both study groups complied with their SHEP prescriptions.

Blood pressure response: Mean systolic BP in the chlorthalidone group decreased from 172 to 146 mm Hg during the first month of treatment, and there was a small further decline over the year of follow-up (Fig. 1). In the placebo group, mean systolic BP decreased to a lesser extent, leaving a net difference between the randomized groups that ranged from 10 to 13% during the year. (The early decline in the placebo group is attributed chiefly to regression to the mean.) Mean diastolic BP also fell during the first month of treatment (from 75 to 70 mm Hg) and the contrast between randomized groups ranged from 5 to 8% during the year.

The 17 mm Hg difference in mean systolic BP between randomized groups after 1 year of follow-up, the point in time specified in our 1-tailed intention-to-treat hypothesis, was highly significant ($p < 0.001$). Stratification revealed no major differences in the magnitude of BP response in various age, race and sex subgroups (Table III). An analysis that was not by intention to treat, i.e., restricted to participants who were taking SHEP medications at annual visit, also revealed a difference of 17 mm Hg for systolic BP and 6 mm Hg for diastolic BP.

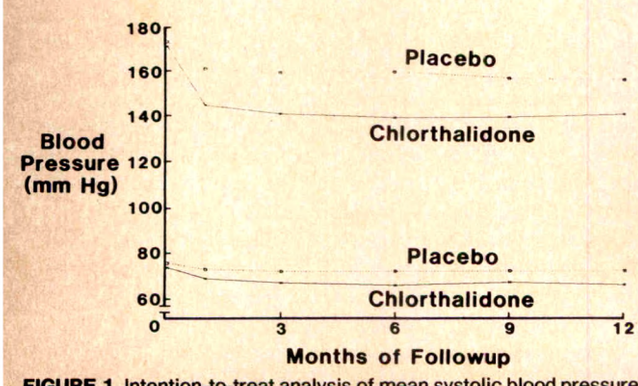

FIGURE 1. Intention-to-treat analysis of mean systolic blood pressure (BP) (**upper curves**) and diastolic BP (**lower curves**). Data represent the visit closest to the indicated time from randomization, within abutting windows of ± 1.5 months (± 0.5 for the 1-month data), and with adjustment for missing data as in Table III.

The distribution of individual BP responses at annual visit (Fig. 2) shows that the response to treatment was uniform. Among those still taking chlorthalidone at annual visit, 88% had not required a step II drug, and 56% were still at the lower (25-mg) dosage. In the placebo group, in contrast, 56% of participants taking SHEP medications at annual visit had advanced to step II (placebo) medication.

BP escape (systolic BP 220 mm Hg or higher or diastolic BP 100 mm Hg or higher) occurred in 4 (1%) participants assigned to chlorthalidone and 8 (7%) participants assigned to placebo. The BP returned to satisfactory levels in all, although 3 of the chlorthalidone and 4 of the placebo participants terminated their SHEP medications and began taking drugs prescribed by their personal physicians.

Symptoms: One month after beginning SHEP medications, the aggregate prevalence of reporting 1 or more troublesome or intolerable symptoms was similar to the baseline finding (about one-third in both study groups) and no symptom was significantly more common in the chlorthalidone group (Table IV). After 1 year of follow-up, the aggregate prevalence had increased somewhat, but remained comparable in the 2 study groups. An analysis restricted to those still taking SHEP medications also revealed no significant excess at 1 year in the chlorthalidone group. Problems in sexual function were reported by 6% of the men in the chlorthalidone

TABLE III Blood Pressure After One Year of Follow-Up by Age, Sex, Race and Study Group—Intention-to-Treat Analysis Adjusted for Missing Data

	No. of Participants*		Systolic BP (mm Hg)			Diastolic BP (mm Hg)		
	Chlorthalidone	Placebo	Chlorthalidone	Placebo	Difference	Chlorthalidone	Placebo	Difference
Age 60–69	176	38	140	159	19†	70	78	8*
70–79	200	56	142	158	16†	67	72	5*
80+	67	14	142	160	18†	63	70	7*
Women	279	70	142	158	16†	66	72	6*
Men	164	38	139	158	19†	69	76	7*
White	365	87	141	157	16†	68	74	6*
Non-white	78	21	142	165	23†	67	71	4
Overall	443	108	141	158	17†	68	74	6*

All statistics are computed by study group assignment, regardless of whether the participant continued to take SHEP medications.
* The measured BP was used for those attending the annual visit (n = 401 in chlorthalidone and n = 104 in placebo groups), and the closest preceding value was substituted for those who did not attend.
† $p < 0.01$ (1-tailed not adjusted for multiple comparisons).
BP = blood pressure; SHEP = Systolic Hypertension in the Elderly Program.

group and none of the men in the placebo group, but the contrast did not reach statistical significance.

Events that were believed possibly drug-related by the blinded SHEP clinicians contributed to the decision to terminate SHEP medications in 7 participants assigned to the chlorthalidone group (3 had dizziness on standing, 1 syncope on standing, 1 a rash, 1 hyperglycemia and 1 complained of problems in sexual function) and in 2 participants assigned to the placebo group (1 developed asthma and 1 had blood pressure escape).

Serum biochemistry levels: After 4 weeks of SHEP medications, mean potassium levels had fallen from 4.5 to 3.9 mEq/liter in the chlorthalidone group ($p < 0.001$) and remained unchanged (at 4.4 mEq/liter) in the placebo group. Levels below 3.5 mEq/liter occurred in 21% of the chlorthalidone group, and levels below 3.0 mEq/liter in 1%. By the annual visit clinicians had elected to prescribe potassium supplements to 13% of the chlorthalidone group and 4% of the placebo group (all of the latter had terminated SHEP medications and been given a diuretic drug by their personal physicians). The mean potassium level and prevalance of hypokalemia were similar to the 1-month values (Table V). Of the 16% with levels below 3.5 mEq/liter in the chlorthalidone group, 46% were at the 50-mg/day dosage. The distribution of individual responses is shown in Figure 3.

Serum creatinine level after 1 year of follow-up was slightly higher in the chlorthalidone group (1.10 vs 1.02 mg/dl, $p = 0.02$), and the proportion with a serum creatinine level 2.0 mg/dl or greater increased slightly in both groups (possibly owing to regression to the mean, because a level below 2.0 mg/dl was a requirement for entering the study). Only 1 person reached a level above 3.0 mg/dl; this patient, whose level was 4.5 mg/dl, was in the chlorthalidone group.

Serum uric acid level was substantially higher in the chlorthalidone group at annual visit (6.8 vs 5.9 mg/dl, $p < 0.001$), but acute gout developed in only 1 chlorthalidone-treated person. Serum cholesterol levels were not significantly altered by the treatment assignment. The nonfasting serum glucose level was slightly higher in the chlorthalidone group ($p = 0.09$), and there was 1 instance of glucose intolerance that required treatment.

Discussion

We conclude that chlorthalidone treatment of elderly patients with isolated systolic hypertension is acceptable to most and produces a substantial lowering of BP. These conclusions from our randomized double-blind study are compatible with the similar findings of the European Working Party High Blood Pressure in the Elderly Trial,[18] the results of nonrandomized studies

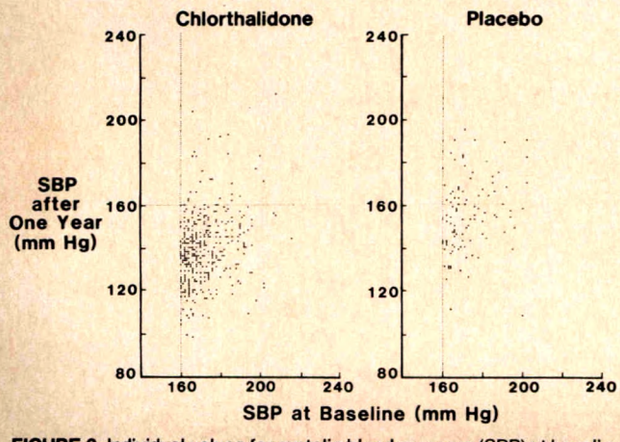

FIGURE 2. Individual values for systolic blood pressure (SBP) at baseline and 1 year after starting chlorthalidone therapy (**left,** n = 401) or placebo (**right,** n = 104).

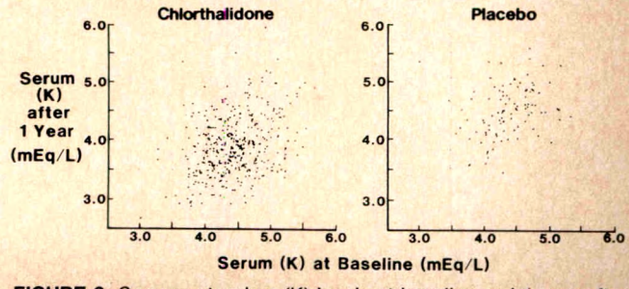

FIGURE 3. Serum potassium (K) levels at baseline and 1 year after starting chlorthalidone therapy (**left,** n = 399) or placebo (**right,** n = 102).

TABLE IV Prevalence of Symptoms Characterized as Troublesome or Intolerable at Baseline and During Follow-Up by Study Group

	Baseline			1 Month			1 Year		
	Chlorthalidone (n = 443)	Placebo (n = 108)	Significance of Difference	Chlorthalidone (n = 443)	Placebo (n = 108)	Significance of Difference	Chlorthalidone (n = 423)	Placebo (n = 107)	Significance of Difference
Cardiopulmonary									
Faintness on standing	3%	4%		3%	5%		5%	7%	
Heart beating fast or skipping	3%	0	p = 0.08	2%	1%		3%	7%	p = 0.05
Chest pain or heaviness	3%	2%		2%	2%		4%	4%	
Unusual shortness of breath	2%	3%		2%	2%		5%	3%	
Unusual tiredness	5%	3%		7%	5%		7%	9%	
Cold or numb hands	2%	2%		1%	0		5%	7%	
Ankle swelling	5%	2%		2%	1%		4%	7%	
Psychosocial									
Depression that interfered with activities	1%	2%		2%	1%		4%	6%	
Nightmares	1%	1%		1%	0		1%	2%	
Problems in sexual function	1%	1%		2%	1%		2%	0	
Problems in sleeping	8%	7%		3%	6%		10%	10%	
Unusual worry or anxiety	5%	3%		3%	3%		7%	10%	
Loss of appetite	0	0		2%	1%		2%	2%	
Other									
Nausea or vomiting	2%	0		5%	2%		2%	2%	
Skin rash or bruising	3%	2%		1%	1%		5%	7%	
Usual joint pain	10%	14%		4%	7%		12%	18%	
Severe headaches	3%	1%		3%	1%		3%	3%	
Excessive thirst	1%	0		1%	0		1%	1%	
Stuffy nose	5%	5%		4%	4%		8%	9%	
Other	3%	5%		10%	11%		11%	18%	p = 0.06
Summary status									
Any of above	30%	33%		34%	31%		44%	48%	
Any of above characterized as intolerable	2%	3%		2%	2%		3%	6%	

The number of observations at 1 year is larger than the number attending the 1-year clinic visit because it includes persons in whom these symptoms were queried by telephone.

Statistical significance of the contrasts between study groups was computed as in Table I and is shown in the table if nominal 2-tailed $p < 0.10$.

TABLE V Serum Biochemistry Values at Baseline and After One Year of Follow-Up by Study Group

	Baseline		1 Year		
	Chlorthalidone (n = 443)*	Placebo (n = 108)	Chlorthalidone (n = 399)*	Placebo (n = 102)*	Significance of Difference
Serum potassium (mEq/liter)					
Mean ± SD	4.4 ± 0.4	4.4 ± 0.4	3.9 ± 0.5	4.5 ± 0.4	<0.001
% <3.5	1.3%	0.9%	15.7%	0.9%	<0.001
% <3.0	0	0	1.5%	0	
Serum creatinine (mg/dl)					
Mean ± SD	1.05 ± 0.21	1.04 ± 0.22	1.10 ± 0.32	1.02 ± 0.22	0.02
% ≥2.0	0	0	1.7%	0.9%	
Serum uric acid (mg/dl)					
Mean ± SD	5.7 ± 1.2	5.6 ± 1.3	6.8 ± 1.5	5.9 ± 1.4	<0.001
Serum glucose (mg/dl)					
Mean ± SD	110 ± 35	108 ± 33	111 ± 40	104 ± 28	0.09
Serum cholesterol (mg/dl)					
Mean ± SD	238 ± 42	242 ± 39	238 ± 46	243 ± 41	

* The number of observations (slightly smaller at 1 year than the number attending clinic because of 5 missing sera) are for all biochemistry values except cholesterol, for which the number at baseline was 439 and 108, and at 1 year 385 and 98, in the chlorthalidone and placebo groups, respectively.

Statistical significance of the contrasts between study groups was computed as in Table I, and is shown in the table if nominal 2-tailed $p < 0.10$; none of the contrasts at baseline reached this level of significance.

SD = standard deviation.

of isolated systolic hypertension treatment in the elderly[19,20] and the results of randomized but non-double-blind trials of diastolic hypertension treatment in the elderly.[21,22]

Although the level of compliance in our study was high, it is difficult to estimate how this would translate to ordinary treatment in the general population. Our choice of relatively healthy and well-motivated volunteers may have enhanced the degree of compliance. However, some instances of discontinuation of SHEP medications may have been a result of participants' concerns about the possibility that they were receiving a placebo.

An unanticipated finding was the efficacy of chlorthalidone as a sole drug for lowering BP; among those still receiving SHEP medications at the annual visit, 88% had reached goal without recourse to step II drugs, and usually required only 25 mg/day. Even lower doses may be effective, and we will be reporting on dosage reduction to a level of 12.5 mg/day of chlorthalidone in a study carried out during the second and third years of follow-up.

A common biochemical effect of chlorthalidone was hypokalemia, with potassium levels below 3.5 mEq/liter in about one-fifth of the chlorthalidone-treated group. SHEP clinicians elected potassium supplementation for many of these participants. Potassium levels below 3.0 mEq/liter were rare, however, and the clinical importance of the moderate chlorthalidone-induced potassium depletion observed in this and other studies of diuretic drugs[23–25] is uncertain. Some studies[24,26] of diuretic treatment show an increase in the rate of ventricular premature complexes and other arrhythmias, while others[27,28] have not; in either event, the evidence that this may be linked to sudden death or other serious clinical events remains uncertain,[29,30] controversial,[31] and limited to younger age groups than the population reported here.

Another biochemical effect of chlorthalidone was a substantial increase in mean serum uric acid levels. This is a well-known metabolic consequence of diuretic treatment,[18,21] which occasionally causes acute gout (1 such case was observed here) but otherwise has no known clinical implication. A third biochemical effect was a small (0.08 mg/dl) increase in mean serum creatinine level in the group receiving chlorthalidone. A change of similar magnitude, of uncertain clinical importance, has been observed previously.[18,21] We did not observe the small increase in serum cholesterol level that has been noted in other populations.[23,32]

Although our study did not detect an excessive rate of symptoms or morbid events in the chlorthalidone group, this does not establish that the treatment is safe. This study was too small to reveal either a beneficial or an adverse effect of treatment on disease events during the first year of follow-up. We will be reporting on the disease event trends observed in this feasibility study when the 3-year follow-up period is completed. The results from the SHEP main trial will be available in about 5 years.

In the meantime, the inference that the increased risk of coronary heart disease and stroke in patients with isolated systolic hypertension can be reduced by treatment is supported by analogy with the beneficial response in clinical trials of treating diastolic hypertension in populations up to age 70 years[21,22], and older.[33] However, serious adverse effects are possible under some circumstances.[30,34] The advisability of drug treatment for isolated systolic hypertension in elderly populations remains uncertain.[1]

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Doppler Evaluation of Left Ventricular Diastolic Filling in Children with Systemic Hypertension

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To assess left ventricular (LV) diastolic function in children with systemic hypertension, 11 patients with hypertension (mean blood pressure 99 mm Hg) and 7 normal patients (mean blood pressure 78 mm Hg) underwent M-mode echocardiography and pulsed Doppler examination of the LV inflow. From a digitized trace of the LV endocardium and a simultaneous phonocardiogram, echocardiographic diastolic time intervals, peak rate of increase in LV dimension (dD/dt), and dD/dt normalized for LV end-diastolic dimension (dD/dt/D) were measured. Doppler diastolic time intervals, peak velocities at rapid filling (E velocity) and atrial contraction (A velocity), and the ratio of E and A velocities were measured. The following areas under the Doppler curve and their percent of the total area were determined: first 33% of diastole (0.33 area), first 50% of diastole, triangle under the A velocity (A area), and the triangle under the E velocity (E area). The A velocity (patients with hypertension = 0.68 ± 0.11 m/s, normal subjects = 0.49 ± 0.08 m/s), the 0.33 area/total area (patients with hypertension = 0.49 ± 0.09, normal subjects = 0.58 ± 0.08), the A area (patients with hypertension = 0.17 ± 0.05, normal subjects = 0.12 ± 0.03), and the A area/total area (patients with hypertension = 0.30 ± 0.11, normal subjects = 0.20 ± 0.07) were significantly different between groups ($p < 0.05$). M-mode and Doppler time intervals, (dD/dt)/D, E velocity, and the remaining Doppler areas were not significantly different between groups. The normal subjects and patients with hypertension did not differ significantly in echocardiographic LV size and thickness or in percent shortening fraction. This study shows that abnormal patterns of LV diastolic filling occur in children with mild systemic hypertension. These diastolic abnormalities are detectable by mitral valve Doppler ultrasound examination when standard M-mode echocardiographic indexes of diastolic function are still normal and before the development of systolic function abnormalities or LV hypertrophy on the M-mode echocardiogram.

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Several recent echocardiographic and radionuclide studies have demonstrated left ventricular (LV) diastolic filling abnormalities in patients with a variety of cardiac diseases, including coronary artery disease, hypertrophic cardiomyopathy and systemic hypertension.[1–13] With the use of noninvasive indexes of LV relaxation and filling, these studies have shown that diastolic dysfunction often precedes systolic dysfunction and is often detectable in asymptomatic patients.[2,4,14] Some investigators have suggested that diastolic abnormalities are a characteristic finding in adult patients with early hypertensive heart disease.[4,6,10,12]

In this study we assessed LV diastolic function in a group of children with mild systemic hypertension using the noninvasive techniques of M-mode and Doppler echocardiography, identified the most sensitive Doppler indexes of LV relaxation, and compared the M-mode and Doppler techniques in their ability to detect early abnormalities of diastolic compliance.

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Methods

Patients: The patient group included 11 children with systemic hypertension and 7 normal children. The normal group consisted of 3 girls and 4 boys who had no evidence of heart disease on physical examination or on M-mode and 2-dimensional echocardiography. They were 10 to 18 years old (mean 15) and weighed 41 to 73 kg (mean 64). The systolic blood pressure of the normal group at the time of the echocardiographic studies was 111 ± 8 mm Hg (mean ± standard deviation); the diastolic blood pressure was 62 ± 8 mm Hg.

The systemic hypertension group consisted of 6 girls and 5 boys who were randomly selected from the outpatient hypertension clinic. They were 1.4 to 17 years (mean 11) and weighed 8.9 to 75 kg (mean 42). The systolic blood pressure of the hypertension group at the time of the echocardiographic studies was 131 ± 13 mm Hg; the diastolic blood pressure was 82 ± 14 mm Hg. In the hypertension group, 7 children had essential hypertension, and 1 each had William's syndrome, primary aldosteronism, previous repair of coarctation of the aorta and atrophic pyelonephritis. The time interval from the

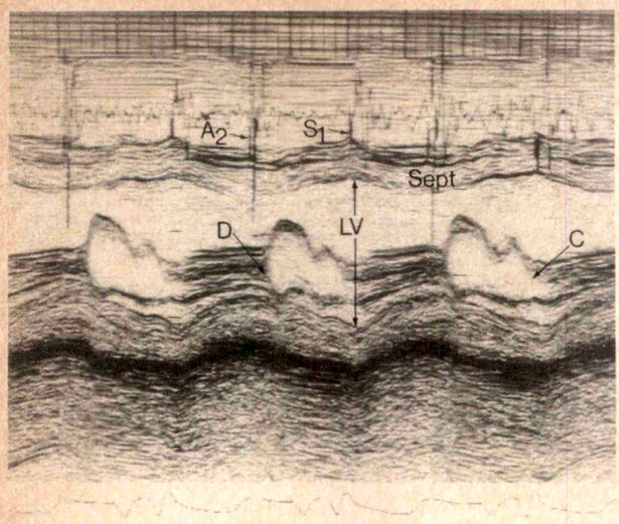

FIGURE 1. M-mode echocardiogram of the left ventricle (LV) with simultaneous phonocardiogram and electrocardiogram. Aortic valve closure (A_2) is the first high-frequency component of the second heart sound. C = mitral valve closure point; D = mitral valve leaflet separation point; S_1 = first heart sound; Sept = septum.

first recorded elevation of the blood pressure to the echocardiographic study ranged from 1 day to 12 years; mean duration of known hypertension was 2.4 years. At the time of the echocardiographic study, 5 patients with hypertension were receiving no medications, 5 were taking diuretic drugs, 3 were receiving β-blocking drugs, 1 was taking captopril and 1 was taking hydralazine.

Echocardiographic examination: Each patient underwent an M-mode echocardiographic examination with a simultaneous phonocardiogram and a pulsed Doppler examination of the LV inflow. M-mode echocardiograms of the left ventricle were generated from the 2-dimensional sector scanner (Advanced Technology Laboratories Mark 600, 3-MHz transducer) using a cursor line positioned at the free edges of the mitral valve leaflets in the parasternal short-axis view (Fig. 1). An unfiltered phonocardiogram was obtained from the second left intercostal space and was recorded simultaneously with the M-mode echocardiogram and an electrocardiogram at a paper speed of 50 mm/s. A record was considered adequate for analysis only when the septal and posterior wall echoes and the time point D of mitral leaflet separation could be clearly identified for at least 3 entire cardiac cycles. Using a hand-controlled pen and a microprocessor system (Digisonics), the echocardiograms were digitized by tracing the endocardial echoes of the septum and the posterior wall.[15–17] From the digitized tracings, a computer printout of the absolute values of the LV minor axis dimension and the rate of change of this dimension with respect to time was available at 3-ms intervals.

From the M-mode echocardiograms, the septum, LV posterior wall and LV dimension were measured at end-diastole at the onset of the QRS wave.[18] LV dimension at end-systole was measured as the smallest systolic dimension from the digitized recording. The shortening fraction, the peak rate of increase in dimension (dD/dt), and the peak rate of increase in dimension normalized for LV end-diastolic dimension (dD/dt/D) were recorded. The normalization of the lengthening velocity, achieved by dividing the peak dD/dt by the LV end-diastolic dimension, allowed comparison of lengthening velocities between different-sized ventricles.[17] The following time intervals were measured from either the original M-mode echocardiogram or the digitized tracings[3,17]:

1. The cardiac cycle length was measured as the time interval between the peaks of 2 successive R waves on the electrocardiogram.
2. The isovolumic relaxation time was measured from the first high-frequency deflection of the aortic closure sound to the initial separation or D point of the mitral valve leaflets.
3. Protodiastole was measured from the point when −dD/dt reaches 0 (the minimum LV systolic dimension) to the aortic closure sound.
4. The total relaxation time was measured from the minimal LV systolic dimension to the point when dD/dt decreases to 50% of its peak value. This latter point corresponds roughly to the transition between the rapid filling and slow filling phases of diastole.[3,17]
5. The relaxation time was defined as the time from the minimal LV systolic dimension to peak dD/dt.
6. The rapid filling period was calculated as total relaxation time minus (isovolumic relaxation time + protodiastole).

Doppler examination: Immediately after M-mode examination, each patient underwent a range-gated pulsed Doppler examination of the LV inflow tract. Using the apical 4-chamber view, the Doppler cursor line and sample volume were placed in the mitral valve funnel at an angle as nearly parallel to flow as possible (Fig. 2). The sample volume position was adjusted so as to record the maximal velocity through the mitral valve. This point was usually found at the level of

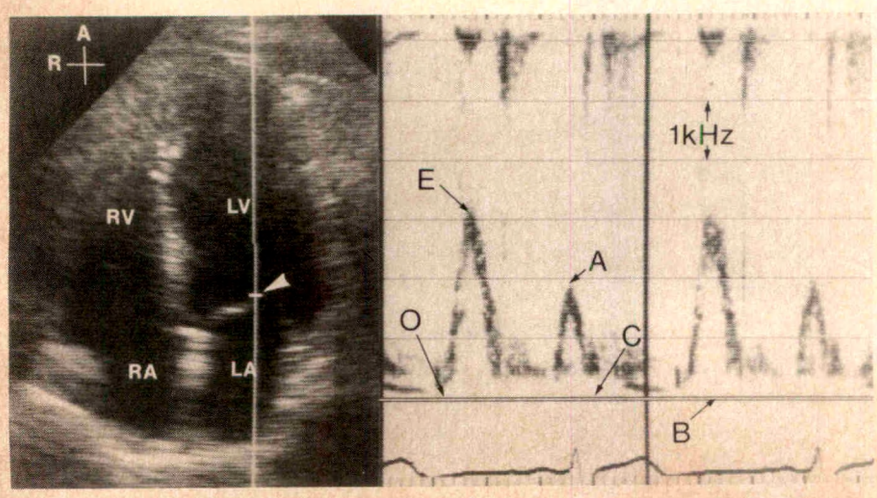

FIGURE 2. Pulsed Doppler spectral recording from the left ventricular inflow. The freeze-frame image of the apical 4-chamber view (**left**) shows the position of the sample volume (**white arrow**) on the Doppler cursor line at the time of the recording. The mitral valve Doppler spectral tracing (**right**) shows forward flow toward the transducer and above the baseline (B) during rapid ventricular filling (E) and atrial contraction (A). C = time point of mitral valve closure; LA = left atrium; LV = left ventricle; 0 = time point of mitral valve opening; RA = right atrium; RV = right ventricle. Orientation: A = anterior, R = right.

the mitral anulus.[19,20] All Doppler examinations were recorded with a 3.0-MHz transducer and a paper speed of 50 mm/s. The Doppler waveform was displayed with frequency shift on the vertical axis, time on the horizontal axis, and amplitude of the signal as shades of gray. Signals from blood flowing toward the transducer were displayed above the baseline and signals from blood flowing away from the transducer were displayed below the baseline. A Doppler examination was considered adequate for analysis only when the opening and closure points (0 and C points) of the mitral valve and the peak velocities at rapid ventricular filling (E point) and during atrial contraction (A point) could be identified for at least 3 cardiac cycles. The following Doppler time intervals were measured: the R to R interval, the time between the 0 to C points, 0 to E points, 0 to A points, the time between the 0 point and the point where the velocity decreases to 50% of its peak E value (which would be expected to correspond to the rapid filling period), the pressure half-time,[21] and the time between the 0 point and the point where the velocity decreases to the value of peak E/1.4. This latter point (where the velocity decreased to peak E/1.4) represents the time at which the LV diastolic pressure decreases to one-half of its peak value during rapid ventricular filling.[21] The interval between the 0 point and peak E/1.4 was included as another technique for measuring the rapid filling period. Also, from the Doppler spectral tracing, the peak E velocity, the peak A velocity, and the ratio of the peak E and peak A velocities were determined.

Because of the changes in the mitral valve cross-sectional area that occur throughout diastole, determination of the absolute volumetric flow in the different portions of diastole would be extremely difficult. Therefore, the Doppler patterns of LV filling were examined by integrating several areas under the Doppler spectral tracing (Fig. 3). The measured areas included the total area under the curve in diastole or the velocity time integral, the area under the curve for the first 50% of diastole, and the area under the curve for the first 33% of diastole (0.33 area). The E area and the A area were measured as the triangular portion under the Doppler curve formed by extrapolating a straight line down from the peak E and peak A velocities to the baseline. To determine the percent of the total velocity time integral occupied by the individual areas and to normalize the data for differences in preload and diastolic cycle lengths among the patients, each individual area was divided by the total area to obtain the area fractions:

$$\text{Area fraction} = \frac{\text{individual Doppler area}}{\text{total Doppler area}}$$

All Doppler areas were measured using a hand-controlled crosswire cursor and a microprocessor system (Microsonics CAD 888) with a spatial resolution of 0.1 mm. The recordings were traced along the densest portion of the Doppler curve and were extrapolated through the area of the wall filter setting to the baseline.

Data analysis: All M-mode and Doppler measurements reported are the average of 3 or more cardiac cycles. Statistical comparisons between the normal group and the hypertension group were made using an unpaired t test. A 2-tailed p value <0.05 was used to indicate a significant difference between groups. All values are reported as mean ± standard deviation. The relation between 2 variables was assessed by linear regression analysis; $p < 0.05$ was considered a significant correlation.

The beat-to-beat variation coefficients for selected diastolic measurements were calculated from 3 successive cardiac cycles of 6 studies (3 normal subjects and 3 patients with hypertension). The variation coefficients were: isovolumic relaxation time, 8.8%; (dD/dt)/D, 6.5%; the total area under the Doppler curve, 2.4%; the Doppler 0.33 area, 4.9%; the A area, 3.8%, the peak A velocity, 4.2%. To determine the interobserver variability, 6 records (3 normal subjects and 3 patients with hypertension) were analyzed independently by 2 observers. The mean percent error between the 2 observers [(first observer − second observer)/average of both observers] × 100, was as follows for selected diastolic measurements: isovolumic relaxation time, 9.8%; (dD/dt)/D, 4.9%; the total area under the Doppler curve, 2.8%; the Doppler 0.33 area, 2.4%; the A area, 3.8%; and the peak A velocity, 2.1%.

TABLE I Blood Pressure and Left Ventricular Measurements in Normal Subjects and Patients with Hypertension

Measurement	Normal Subjects	Patients with Hypertension	p Value
Systolic BP (mm Hg)	111 ± 8	131 ± 13	0.004*
Diastolic BP (mm Hg)	62 ± 8	82 ± 14	0.006*
LVDD (cm)	5.11 ± 0.45	4.36 ± 1.02	0.09
LVSD (cm)	3.04 ± 0.43	2.52 ± 0.65	0.08
SF	0.41 ± 0.06	0.42 ± 0.05	0.55
LVPW (cm)	0.81 ± 0.16	0.79 ± 0.19	0.77
Septum (cm)	0.77 ± 0.13	0.76 ± 0.20	0.89

* Statistically different between groups at the 5% level.
Values are mean ± standard deviation.
BP = blood pressure; LVDD = left ventricular end-diastolic dimension; LVPW = left ventricular posterior wall thickness; LVSD = left ventricular end-systolic dimension; SF = shortening fraction.

Results

A significant difference was found in the systolic and diastolic blood pressures between the 2 groups

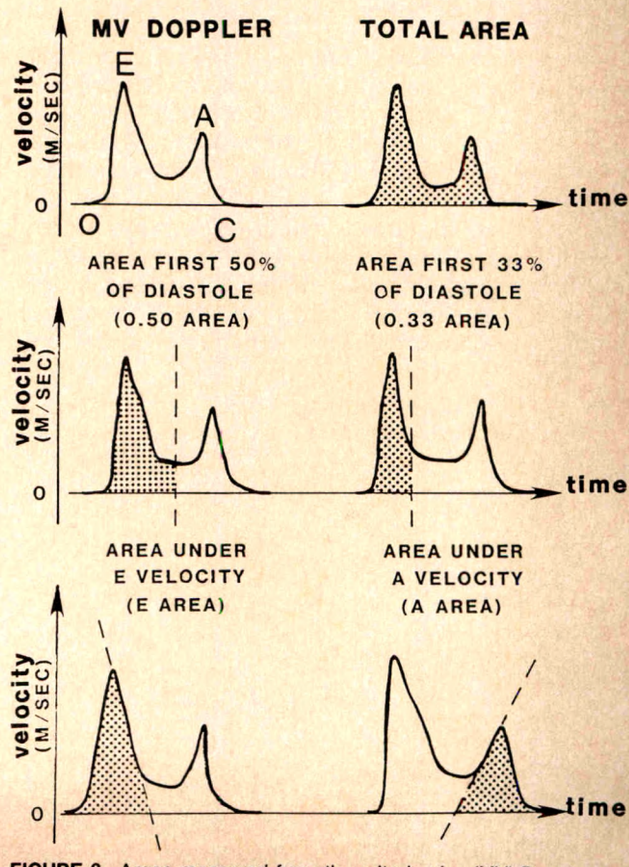

FIGURE 3. Areas measured from the mitral valve (MV) Doppler recordings. Abbreviations as in Figure 2.

TABLE II M-Mode Echocardiographic Measurements

Measurement	Normal Subjects	Patients with Hypertension	p Value
RR interval (s)	0.88 ± 0.12	0.78 ± 0.20	0.28
Isovolumic relax. time (s)	0.03 ± 0.01	0.04 ± 0.01	0.08
Total relax. time (s)	0.16 ± 0.04	0.14 ± 0.05	0.57
Relax. time (s)	0.10 ± 0.04	0.08 ± 0.04	0.22
Rapid filling period (s)	0.10 ± 0.06	0.12 ± 0.07	0.67
Peak dD/dt (cm/s)	10.44 ± 2.50	10.88 ± 4.30	0.80
(dD/dt)/D (s^{-1})	2.09 ± 0.34	2.66 ± 0.94	0.14

Values are mean ± standard deviation.
dD/dt = peak rate of increase in left ventricular dimension in diastole; (dD/dt)/D = peak rate of increase in left ventricular dimension normalized for end-diastolic dimension; relax. = relaxation; RR = cardiac cycle length.

TABLE III Mitral Valve Doppler Measurements

Measurement	Normal Subjects	Patients with Hypertension	p Value
RR interval (s)	0.94 ± 0.21	0.77 ± 0.14	0.06
0 to C (s)	0.52 ± 0.20	0.36 ± 0.11	0.06
0 to E (s)	0.10 ± 0.01	0.08 ± 0.02	0.09
0 to A (s)	0.47 ± 0.21	0.31 ± 0.10	0.06
0 to E/2 (s)	0.16 ± 0.01	0.16 ± 0.08	0.85
Pressure half-time (s)	0.04 ± 0.01	0.03 ± 0.01	0.62
0 to E/1.4 (s)	0.13 ± 0.02	0.11 ± 0.02	0.15
Peak E (m/s)	0.91 ± 0.11	1.00 ± 0.16	0.20
Peak A (m/s)	0.49 ± 0.08	0.68 ± 0.11	0.002*
Ratio peak E/peak A	1.87 ± 0.39	1.52 ± 0.43	0.095

* Statistically different between groups at the 5% level.
Values are expressed as mean ± standard deviation.
A = velocity at atrial contraction; C = time point of mitral valve closure; E = velocity during rapid ventricular filling; 0 = time point of mitral valve opening; RR = cardiac cycle length.

(Table I); however, no differences were found in the LV dimensions, shortening fraction or LV thickness between the 2 groups. The M-mode time intervals, peak dD/dt, and (dD/dt)/D were not different between groups (Table II). The isovolumic relaxation time was the only M-mode measurement that approached being significantly different between groups (Table II). Similarly, the Doppler diastolic time intervals were not significantly different between groups (Table III). Attempts at normalizing the M-mode and Doppler diastolic time intervals by dividing the time

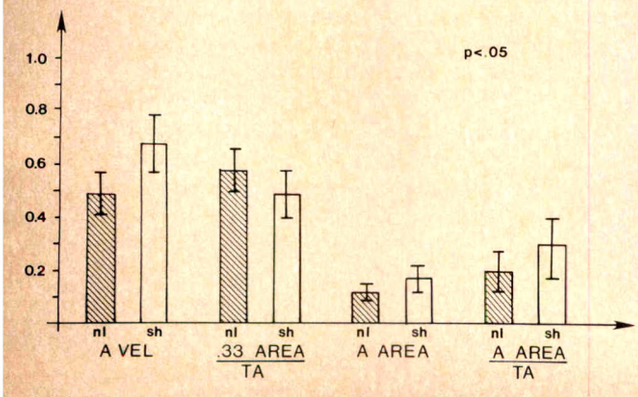

FIGURE 4. The Doppler measurements that differentiated the normal group (nl) from the hypertension group (sh). TA = total area under the Doppler curve; VEL = velocity; other abbreviations as in Figure 3.

TABLE IV Mitral Valve Doppler Areas

Measurement	Normal Subjects	Patients with Hypertension	p Value
Total area	0.60 ± 0.15	0.58 ± 0.11	0.68
0.50 area	0.42 ± 0.14	0.38 ± 0.10	0.51
0.50 area/total area	0.69 ± 0.05	0.66 ± 0.07	0.28
0.33 area	0.36 ± 0.13	0.28 ± 0.08	0.14
0.33 area/total area	0.58 ± 0.08	0.49 ± 0.09	0.04*
E area	0.39 ± 0.10	0.40 ± 0.11	0.80
E area/total area	0.65 ± 0.04	0.69 ± 0.09	0.26
A area	0.12 ± 0.03	0.17 ± 0.05	0.02*
A area/total area	0.20 ± 0.07	0.30 ± 0.11	0.05*

* Statistically different between groups at the 5% level.
Values are expressed as mean ± standard deviation.
Abbreviations as in Table III.

interval by the cycle length did not change these results.[10] The peak A velocity of the systemic hypertension group was significantly higher than that of the normal subjects ($p = 0.002$).

With regard to the mitral valve area measurements (Table IV), the percent of the total area in the first third of diastole was significantly lower in the systemic hypertension group ($p = 0.04$). The A area and the percent of the total area under the A wave were significantly higher in the patients with hypertension ($p = 0.02$ and 0.05, respectively). With regard to M-mode and Doppler measurements, the only measurements that separated patients with systemic hypertension from normal subjects were the Doppler A-wave velocity, the Doppler A area, and the percent of the Doppler total area in the first one-third of diastole and under the A wave (Fig. 4). To determine if any of these 4 variables correlated with the severity of the hypertension, linear regression analysis was performed on the data pooled from both patient groups. There was no significant correlation between these 4 variables and systolic blood pressure, diastolic blood pressure, LV posterior wall thickness or septal thickness. Also, in the patients with hypertension, there was no correlation between the blood pressure and LV thickness.

Discussion

In adult patients with chronic hypertension, M-mode echocardiographic studies have shown diminished early peak LV diastolic filling rates, prolonged isovolumic relaxation time and shortened rapid filling period.[2,11,12,14] Similarly, radionuclide studies in adult patients with hypertension have revealed decreased early peak diastolic filling rates and decreased percent LV filling in the first one-third of diastole.[10,11] This study shows that abnormal patterns of LV diastolic filling occur in children with mild systemic hypertension and that these diastolic filling abnormalities are detectable by mitral valve Doppler examination when standard M-mode indexes of diastolic function are still normal and before the development of systolic function abnormalities or LV hypertrophy on the M-mode echocardiogram.

The decrease in the percent of the total area in the first one-third of diastole and the increase in the percent of the total area under the A wave in the children with hypertension suggest a relative shift of LV filling to late

diastole.[2,10] The impaired LV filling in early diastole was accompanied by a compensatory increase in LV filling in late diastole (during atrial contraction) so that the LV end-diastolic dimension and total area under the Doppler curve of the hypertension group were normal.

M-mode versus Doppler findings: In this study, abnormalities of diastolic filling were more easily recognized by mitral valve Doppler examination than by M-mode echocardiographic techniques. Several explanations are possible for this difference. First, even though the M-mode echocardiograms were obtained while imaging the LV minor axis, slight variations in the level of the cross-sectional plane from which the echocardiogram is obtained greatly influence measurements of the diastolic relaxation times and filling rates.[17,22] Second, the M-mode measurements vary considerably from beat to beat and with different observers. Despite this variability, the echocardiographic relaxation times and filling rates of our normal patients were similar to values reported by others.[3,17] Third, Bahler et al[17] showed that the time course of diastolic relaxation is dependent on cardiac cycle length; however, the velocity of relaxation is independent of cycle length. This factor may explain why diastolic filling abnormalities were more easily detectable with the Doppler indexes (which are velocity measurements) than with echocardiographic relaxation time indexes. Bahler reported that the isovolumic relaxation time is the time interval that is most independent of cycle length.[17] In our study, the isovolumic relaxation time was the only echocardiographic measurement that came close to being significantly different between the 2 groups. This finding further suggests that the remaining echocardiographic time indexes were influenced by heart rate and, therefore, were not useful in differentiating normal subjects from patients with hypertension.

There was far less beat-to-beat and interobserver variability in the mitral valve Doppler measurements. We have found that good-quality Doppler recordings suitable for analysis are easier to obtain than good-quality M-mode recordings suitable for digitizing. This is particularly true in adult patients in whom conditions such as obesity and chronic lung disease may make parasternal echocardiographic examination extremely difficult.

Factors affecting diastolic relaxation indexes: Diastolic indexes of LV relaxation can be influenced by several factors including heart rate and LV loading conditions.[23–25] Bahler et al[17] showed that the rapid filling phase occupies an increasing proportion of diastole as heart rate increases. Studies in the intact heart have shown that the duration of relaxation and the velocity of lengthening are intimately related to the velocity of shortening and the inotropic state.[26–30] In this study, differences in the diastolic filling patterns between the normal and the hypertension group cannot be explained on the basis of differences in heart rate, systolic function or LV loading conditions. The heart rates of the 2 groups were not different, either at the time of the M-mode examination or at the time of the Doppler examination. The systolic function of the 2 groups, as assessed by the M-mode shortening fraction, was normal. The LV end-diastolic dimensions of both patient groups were statistically similar, indicating no intergroup differences in ventricular loading conditions. Also, division of the individual Doppler areas by the total area under the Doppler curve and division of dD/dt by the LV end-diastolic dimension normalized these measurements for differences in preload.

Possible mechanisms and clinical implications of diastolic filling abnormalities: The abnormal diastolic filling noted in patients with systemic hypertension could be a result of (1) increased LV chamber stiffness caused by LV hypertrophy with normal myocardial stiffness or (2) decreased LV compliance caused by myocardial dysfunction or fibrosis.[10,25,31] The patients with hypertension in our study showed diastolic filling abnormalities in the presence of normal septal and posterior wall thicknesses. Possible explanations for this finding are that (1) diastolic abnormalities occur early in the course of systemic hypertension, even preceding development of LV hypertrophy, (2) total LV mass may be increased in patients with hypertension even when M-mode measurements show normal wall thickness,[13] or (3) hypertrophy may have already regressed in the patients receiving therapy.

Six patients with hypertension who were receiving antihypertensive therapy at the time of the echo-Doppler study and whose hypertension was under good control still had Doppler diastolic filling abnormalities. Using radionuclide techniques, Inouye et al[13] showed failure of reversal of LV diastolic filling abnormalities in patients with hypertension after therapy with diuretic, β-blocking and calcium channel-blocking drugs. These studies suggest that there may be irreversible changes in diastolic filling patterns that occur early in patients with systemic hypertension.[13,32,33]

Comparison of Doppler, echocardiographic and radionuclide indexes of left ventricular filling: Our values for the Doppler area fractions are very similar to Hanrath's values for percent dimensional increase measured from the echocardiogram and Inouye's values for first-third filling fraction measured from radionuclide techniques.[2,10] Hanrath et al[2] noted in normal subjects that 62 ± 10% of the total change in diastolic dimension occurred during the rapid filling phase of diastole and 16 ± 10% of the total dimensional change occurred during atrial contraction (compared with Doppler area fractions in our normal group of 0.58 ± 0.08 for 0.33 area/total area and 0.20 ± 0.07 for A area/total area). In Hanrath's patients with hypertension, 51 ± 12% of the total dimensional increase occurred during rapid filling and 23 ± 10% of the total dimensional increase occurred during atrial contraction (compared with Doppler area fractions in our hypertension group of 0.49 ± 0.09 for 0.33 area/total area and 0.30 ± 0.11 for A area/total area). Likewise, Inouye et al[10] showed a first-third filling fraction (counts in the first one-third of diastole divided by the total stroke count) of 0.60 ± 0.07 for normal subjects and 0.41 ± 0.13 for hypertensive patients age-matched to control subjects (compared with 0.33 area/total area of 0.58 ± 0.08 for normal subjects and 0.49 ± 0.09 for hypertensive patients).

These studies, using 3 different imaging and measurement techniques, all demonstrate a shift in the LV filling pattern to the latter part of diastole in patients with hypertension.

In conclusion, abnormalities of diastolic filling occur early in children with systemic hypertension, before M-mode evidence of LV hyertrophy and before clinical or echocardiographic evidence of systolic dysfunction. Measurement of diastolic filling patterns from the mitral valve Doppler examination appears to be a useful method of detecting early abnormalities of diastolic function. For assessing diastolic function, the Doppler area measurements appear to have less variability than the echocardiographic diastolic time intervals and filling rates and may allow earlier detection of diastolic filling abnormalities. The Doppler technique should be useful in assessing diastolic function in a wide variety of clinical situations, including the patients with coronary artery disease, myocarditis or cardiomyopathy, LV outflow tract obstruction and previous cardiac transplantation.

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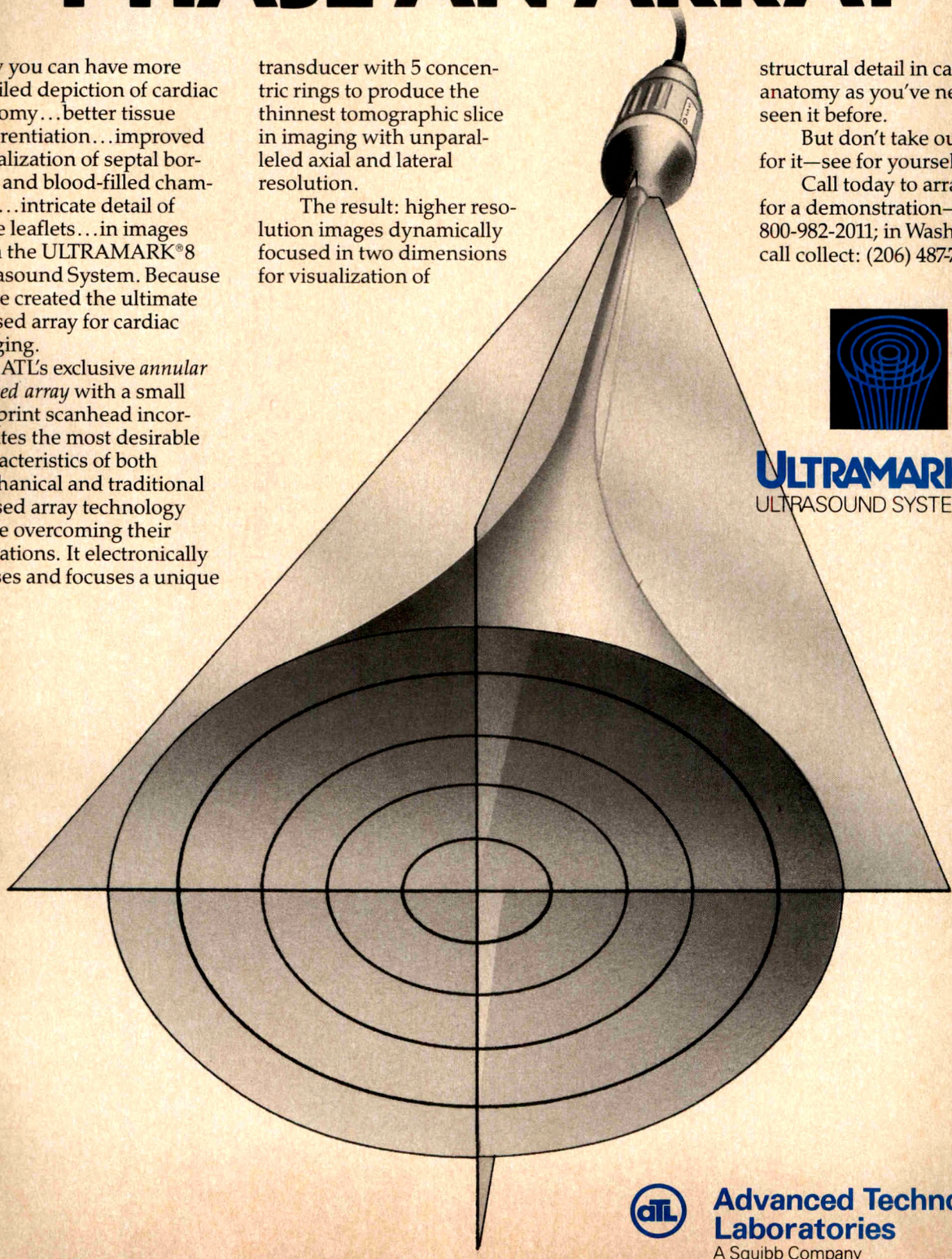

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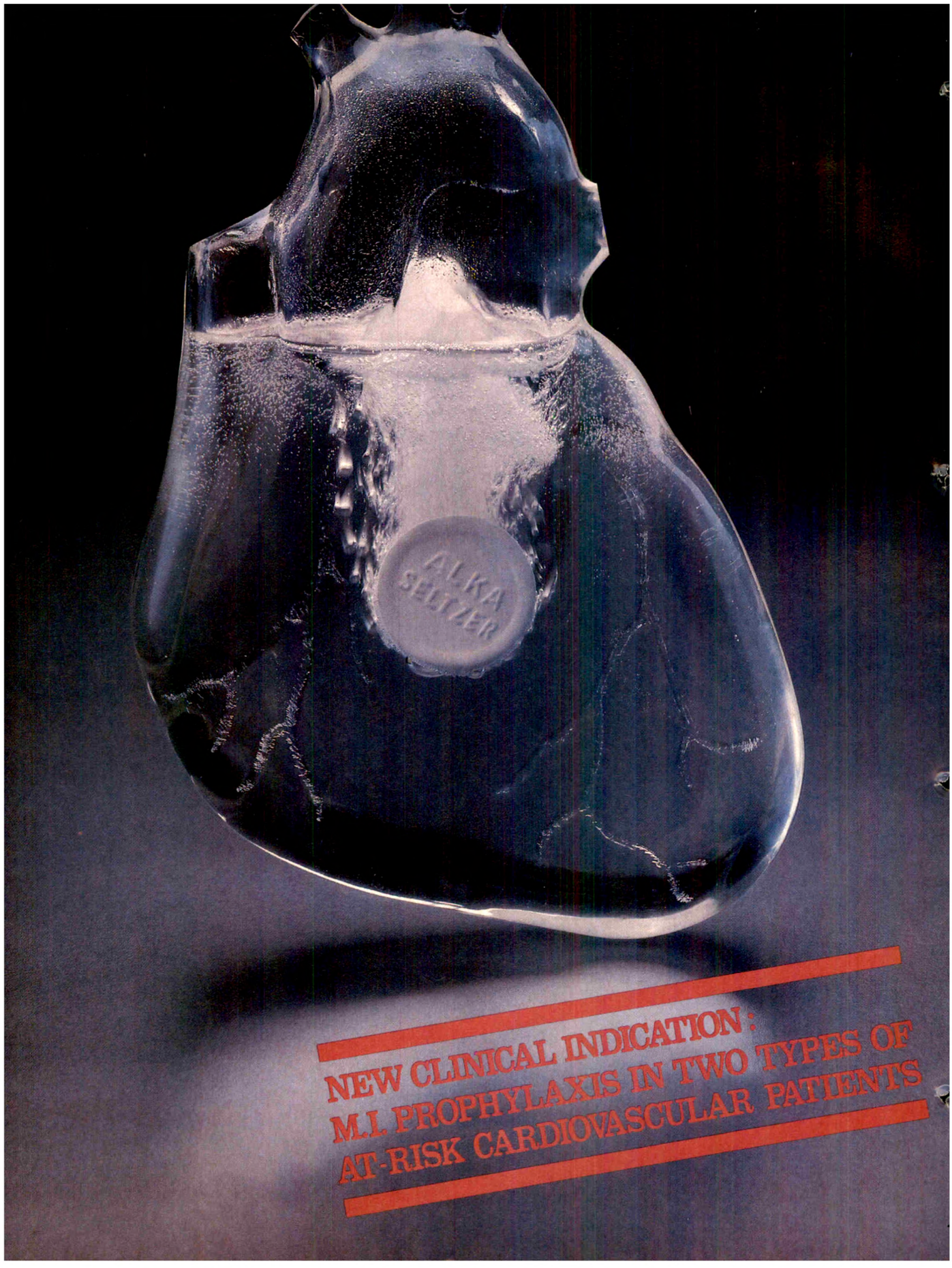
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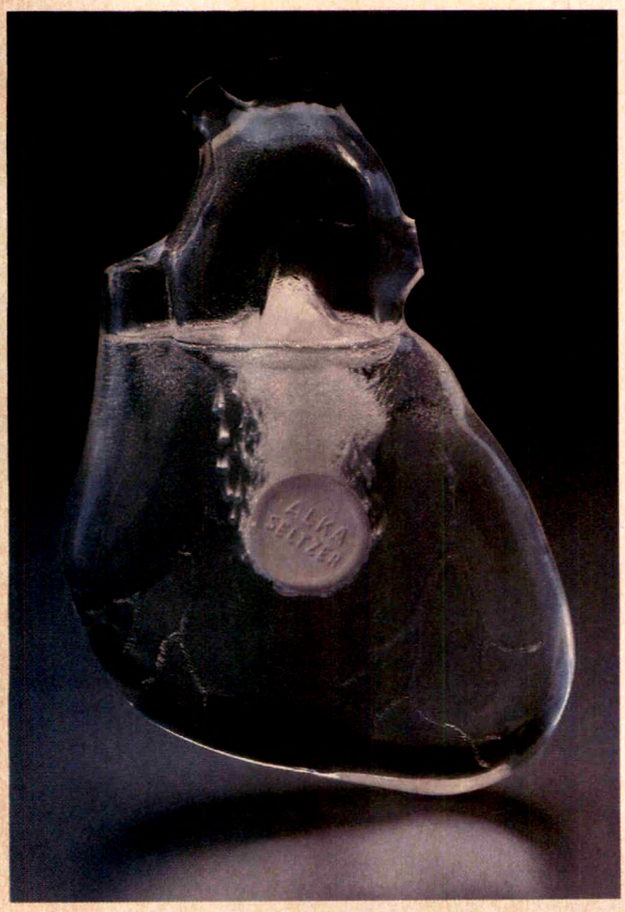
The Analysis: The six clinical studies were reviewed and analyzed by two teams of independent investigators.[9,10]

The Results: The combined results from the six clinical trials indicate that daily ingestion of aspirin reduced the incidence of reinfarction and/or death.



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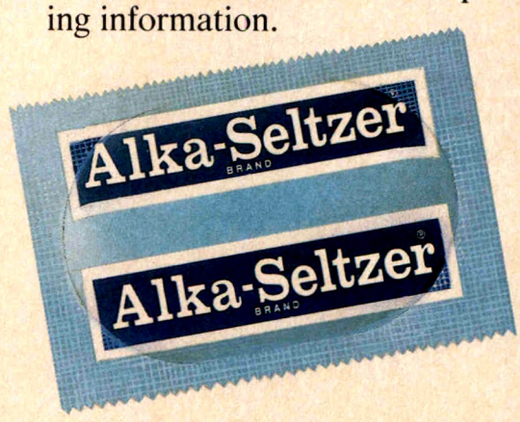

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Clinical Trials:
The indication is supported by the results of six, large, randomized multicenter, placebo-controlled studies[1-7] involving 10,816, predominantly male, post-myocardial infarction (MI) patients and one randomized placebo-controlled study of 1,266 men with unstable angina. Therapy with aspirin was begun at intervals after the onset of acute MI varying from less than 3 days to more than 5 years and continued for periods of from less than one year to four years. In the unstable angina study, treatment was started within 1 month after the onset of unstable angina and continued for 12 weeks and complicating conditions such as congestive heart failure were not included in the study.

Aspirin therapy in MI patients was associated with about a 20 percent reduction in the risk of subsequent death and/or non-fatal reinfarction, a median absolute decrease of 3 percent from the 12 to 22 percent event rates in the placebo groups. In aspirin-treated unstable angina patients the reduction in risk was about 50 percent, a reduction in event rate of 5 percent from the 10 percent rate in the placebo group over the 12 weeks of the study.

Daily dosage of aspirin in the post-myocardial infarction studies was 300 mg in one study and 900 to 1500 mg in five studies. A dose of 325 mg was used in the study of unstable angina.

Adverse Reactions:
Gastrointestinal Reactions: Doses of 1000 mg per day of aspirin caused gastrointestinal symptoms and bleeding that in some cases were clinically significant. In the largest post-infarction study (the Aspirin Myocardial Infarction Study (AMIS) with 4,500 people), the percentage incidences of gastrointestinal symptoms for the aspirin (1000 mg of a standard, solid-tablet formulation) and placebo-treated subjects, respectively, were: stomach pain (14.5%; 4.4%); heartburn (11.9%; 4.8%); nausea and/or vomiting (7.6%; 2.1%); hospitalization for gastrointestinal disorder (4.9%; 3.5%). In the AMIS and other trials, aspirin treated patients had increased rates of gross gastrointestinal bleeding. Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for unstable angina with buffered aspirin in solution.

Cardiovascular and Biochemical:
In the AMIS trial, the dosage of 1000 mg per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 mm) and diastolic BP (0.5 to 0.6 mm), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased, but by less than 1.0 mg%. Subjects with marked hypertension or renal insufficiency had been excluded from the trial so that the clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 300 mg per day, be seen at regular intervals to assess changes in these measurements.

Sodium in Buffered Aspirin for Solution Formulations:
One tablet daily of buffered aspirin in solution adds 553 mg of sodium to that in the diet and may not be tolerated by patients with active sodium-retaining states such as congestive heart or renal failure. This amount of sodium adds about 30 percent to the 70 to 90 mEq intake suggested as appropriate for dietary treatment of essential hypertension in the 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[8]

Dosage and Administration:
Although most of the studies used dosages exceeding 300 mg daily, two trials used only 300 mg and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 mg or a conventional 325 mg aspirin dose daily is a reasonable, routine dose that would minimize gastrointestinal adverse reactions. This use of aspirin applies to both solid, oral dosage forms (buffered and plain aspirin) and buffered aspirin in solution.

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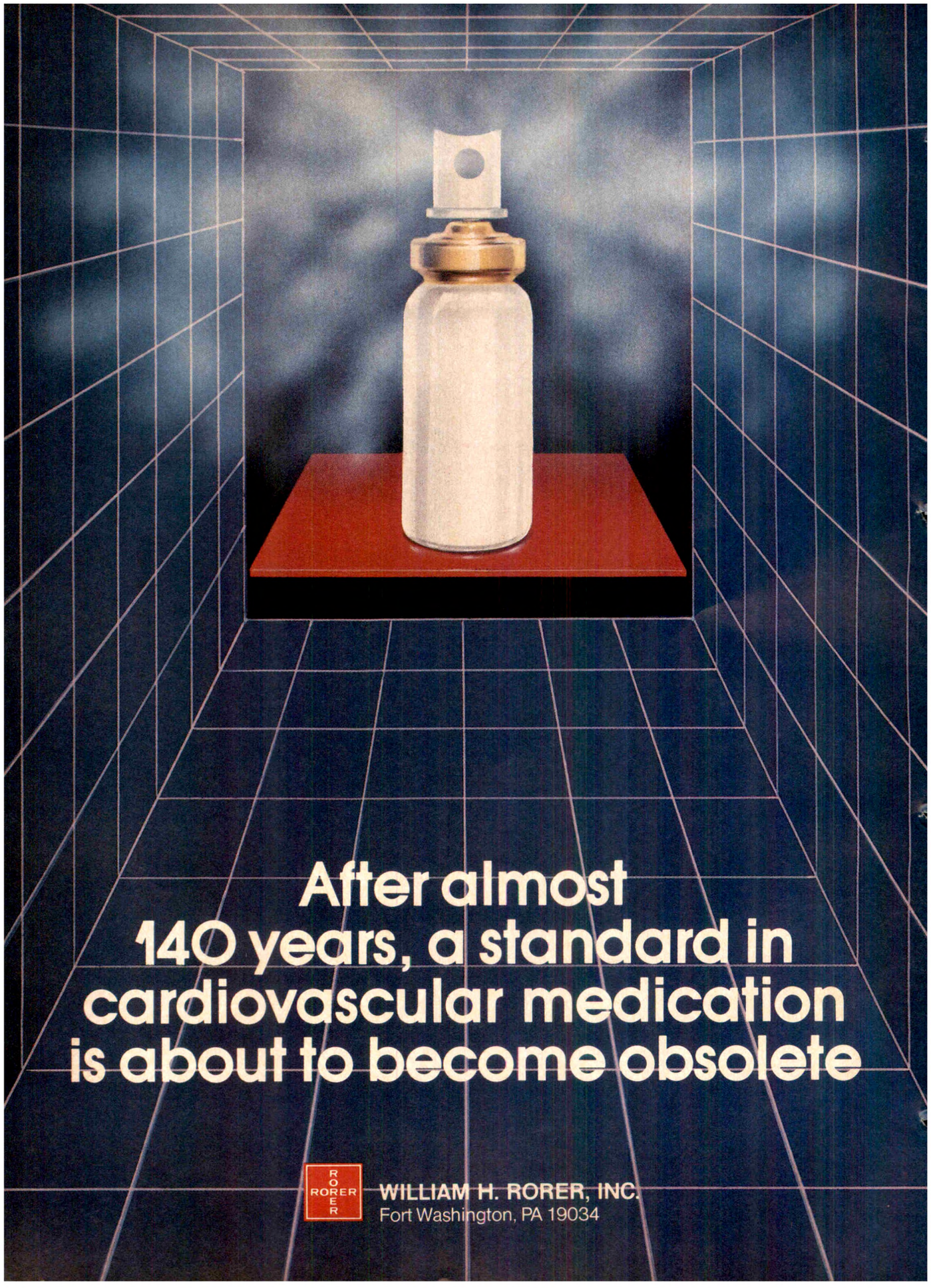
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Systemic Hypertension After Cardiac Transplantation: Effect of Cyclosporine on the Renin-Angiotensin-Aldosterone System

MARC BELLET, MD, CHRISTIAN CABROL, MD, PAOLO SASSANO, MD, PHILIPPE LÉGER, MD, PIERRE CORVOL, MD, and JOËL MÉNARD, MD

Fifteen patients who had undergone cardiac transplantation and who had hypertension (164 ± 14/112 ± 13 mm Hg), aged 16 to 57 years (mean 39), were treated with cyclosporine, 8 ± 3 mg/kg/day, and prednisolone, 0.27 ± 0.1 mg/kg/day, for 63 to 788 days (mean 288) after transplantation. They were not given antihypertensive drugs. Before treatment, the mean urinary sodium level was 104 ± 48 mEq/day. Two discrete abnormalities accompanied their high blood pressure (BP): an increase in serum creatinine levels ($p < 0.05$) to values exceeding those measured just before transplantation (2.1 ± 1.0 vs 1.35 ± 0.54 mg/dl) with low creatinine clearance (61 ± 28 ml/min · 1.73 m^2), and a 15% increase in plasma volume (+445 ± 686 ml, $p < 0.02$). Urinary excretion of vanilmandelic acid and total metanephrines was normal. Supine plasma renin activity was also normal (0.78 ± 0.32 nmol/ml/hour). The stimulation of renin release after acute inhibition of converting enzyme by captopril was less marked than is usual in hypertensive subjects (0.86 ± 0.54 nmol/liter/hour). Captopril induced a smaller drop in BP than nifedipine (−8 ± 13/−6 ± 10 mm Hg vs −14 ± 11/−15 ± 10 mm Hg). Levels of plasma aldosterone, angiotensinogen and converting enzyme activity were all normal, 308 ± 147 pmol/liter, 712 ± 164 nmol/ml and 30 ± 6 mU/ml, respectively. It is concluded that hypertension is common in cardiac transplantation patients treated with cyclosporine, since 13 of our 15 subjects were normotensive before transplant. Further, such hypertension is characterized by an expansion of plasma volume and the absence of major abnormalities of the renin-angiotensin-aldosterone system, despite the potential nephrotoxicity of cyclosporine.

(Am J Cardiol 1985;56:927–931)

Cyclosporine is a potent orally active immunosuppressant drug used in human organ transplantation.[1] One of the most notable adverse effects of cyclosporine therapy is nephrotoxicity. Thus, after several months of therapy with high doses, focal glomerular sclerosis was observed with a low glomerular filtration rate and reduced plasma flow.[2]

Although 2 years after cardiac allografting the survival rate with cyclosporine treatment increased from 58% to 75% compared with conventional immunosuppressive therapy, most of the long-term survivors treated with cyclosporine after cardiac transplantation became hypertensive; this contrasts with the incidence of less than 20% among patients given conventional immunosuppressive therapy.[3] Systemic arterial hypertension has also been reported in patients treated with cyclosporine after bone marrow[4,5] or kidney transplantation.[6] The pathogenesis of this complication is not clear. Animal experiments and in vitro studies suggest that cyclosporine stimulates the renin-angiotensin-aldosterone system.[7,8]

After cardiac transplantation, allograft rejection does not interfere with renal damage caused by this drug, unlike what is observed after kidney transplantation.[9] We therefore investigated the renin-angiotensin-aldosterone system in a group of heart transplant recipients who were hypertensive and were being treated with cyclosporine.

Methods

The study included 15 patients (14 men, 1 woman), aged 16 to 57 years (mean 39). This group of long-term survivors of cardiac transplantation (63 to 788 days) was gleaned from a total of 40 adults who had undergone transplantation at the cardiovascular surgery center of the Pitié Hospital in Paris from October 1981 through January 1984, and were treated with cyclosporine combined with prednisolone.

In 20 of these 40 patients, mild or moderate hypertension developed; 15 of these 20 are the subject of this report. Permanent hypertension was diagnosed in all 15 on the basis of 3 ambulatory blood pressure readings above 140/90 mm Hg. Only 2 patients were known to have mild, intermittent hypertension before cyclosporine treatment. All patients were kept under observation in hospital for 3 days. The nature of the study was explained to them, and each patient gave informed consent. All patients had normal cardiac function

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(New York Heart Association functional class I). Routine tests confirmed that no patient had any of the usual forms of secondary hypertension. Subjects were allowed water ad libidum and free sodium and potassium intake. Patients had either never been treated with antihypertensive drugs or had stopped treatment at least 2 weeks before admission to hospital. Cyclosporine had been administered at a daily dose of 8 ± 3 mg/kg body weight 1 month after surgery until the study and the levels of immunoassayable plasma cyclosporine during the study before the morning dose ranged from 62 to 280 ng/ml (mean 181.4 ± 67.6). Prednisolone was administered at a daily dose of 0.27 ± 0.1 mg/kg body weight.

The following protocol was used. On day 1, heart rates in the supine and upright positions were compared, plasma volume was determined and 24-hour urine samples were measured for volume and excretion of sodium, potassium, creatinine, vanilmandelic acid and total metanephrine (i.e., normetanephrine and metanephrine); standard blood measurements were assessed in samples from fasting patients. On day 2, an automatic Sentron monitor was set at 8 AM on the right arm of recumbent, fasting patients and programmed to record heart rate and blood pressure every 3 minutes until 12 PM. At 8 AM, after 1 hour of standing, venous blood samples were collected for measurement of plasma renin activity and plasma aldosterone. At 9 AM, after 1 hour of recumbency, other blood samples were drawn for estimation of plasma renin activity, plasma aldosterone, angiotensinogen and plasma converting enzyme activity. Finally, captopril was given orally (1 mg/kg body weight) and 3 hours later, plasma renin activity and plasma aldosterone were again measured with the patient still supine. On day 3, the blood pressure and heart rate monitor was again set in recumbent patients from 8 AM to 11 AM. At 9 AM, 1 capsule containing 10 mg of nifedipine was orally ingested by 14 patients. The period of blood pressure recording was shorter after nifedipine than after captopril, as the nadir of blood pressure reduction occurs faster with nifedipine than captopril.[10–12]

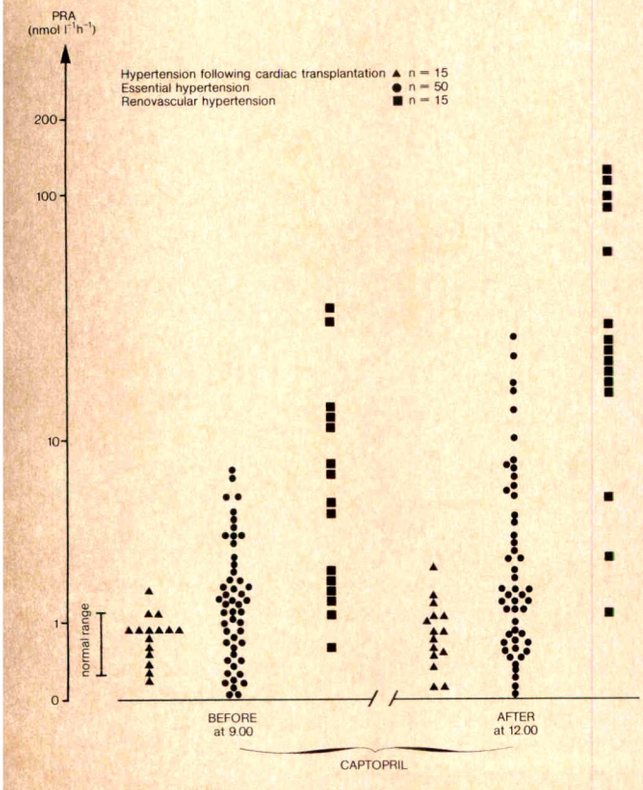

FIGURE 1. Variations in plasma renin activity (PRA) after a single dose of captopril (1 mg/kg body weight) in hypertensive cardiac transplantation patients treated with cyclosporine (**triangles**). Values were compared with those reported for patients with renovascular (**squares**) and essential hypertension (**circles**).[12]

Plasma renin activity and angiotensinogen were measured by angiotensin I radioimmunoassay,[13] plasma-converting enzyme activity was measured by the method of Cusmann modified by Lieberman[14] and plasma aldosterone, by direct radioimmunoassay.[15] Supine plasma volume was measured in 15 patients by the radioiodine-labeled serum albumin method, as previously described[16]; normal values were those reported by Hurley et al.[17] Urinary vanilmandelic acid and total metanephrines were measured by colorimetric and fluorimetric methods respectively. Blood pressure was measured by estimating the area under blood pressure-time curves divided by the period of recording. The maximal variations in heart rate were calculated from the average of the 7 values successively observed during the steepest drop in blood pressure after each drug.

Statistical comparisons were made by the Wilcoxon test for paired data, as appropriate. Correlation coefficients were obtained by the least-squares method. A p value <0.05 was considered statistically significant. Results are expressed as means ± standard deviation.

Results

The characteristics of the patients are given in Table I. After cardiac transplantation, an abnormal increase in serum creatinine levels was noted in 13 patients (2.10 ± 1 mg/dl vs 1.35 ± 0.54 mg/dl before transplantation, $p < 0.05$) combined with low creatinine clearance (61 ± 28 ml/min·1.73 m^2). Plasma volume rose significantly above the normal values measured in healthy volunteers (3,416 ± 687 ml vs 2,971 ± 321 ml, $p < 0.02$).[17] No 24-hour proteinuria was noted. Urinary excretion of vanilmandelic acid and total metanephrines was in the range of our normal laboratory values (less than 40 and less than 37 μmol per 24 hours, respectively).

Renin-angiotensin-aldosterone system: No stimulation of plasma renin activity was observed during cyclosporine treatment, either in the supine or upright positions (0.78 ± 0.32 and 1.97 ± 1.01 nmol/ml/hour, respectively; normal 0.27 to 1.00 and 0.54 to 2.31). After inhibition of converting enzyme, plasma renin activity was 0.86 ± 0.54 nmol/ml/hour and did not increase significantly (Fig. 1). Plasma renin activity values before captopril and 3 hours afterwards were compared with the values previously reported[12] for patients with renovascular and essential hypertension (Fig. 1). Angiotensinogen and plasma-converting enzyme activity were normal, 712 ± 164 nmol/ml (normal 617 to 925) and 30 ± 6 mU/ml (normal 23 to 38) respectively. Plasma aldosterone in the supine position was 308 ± 147 pmol/liter (normal 140 to 336), and after orthostatic stimulation, 1,346 ± 61 pmol/liter (normal 420 to 840). After converting enzyme inhibition, it decreased to 137 ± 61 pmol/liter ($p < 0.01$).

Blood pressure: Nifedipine significantly reduced blood pressure, from 140 ± 13/91 ± 14 mm Hg to 126 ± 13/76 ± 14.5 mm Hg ($p < 0.005$/$p < 0.005$). Captopril reduced it, from 147 ± 19/94.5 ± 17 mm Hg to 139 ± 17/89 ± 15 mm Hg ($p < 0.05$/$p < 0.05$). Although the

decrease in systolic blood pressure after nifedipine was not different from the drop after captopril, diastolic blood pressure fell more steeply after nifedipine ($p < 0.01$) (Fig. 2).

Heart rate: Heart rates in the supine and upright positions were compared in 14 patients. A maximal increase from 85 ± 11 to 98 ± 11 beats/min ($p < 0.02$) was observed after 15 minutes in the upright position, for a drop in blood pressure of 10 ± 13/4 ± 6 mm Hg ($p < 0.02$/$p < 0.05$). The hypotensive action of nifedipine was accompanied by tachycardia; heart rate increased from 83 ± 10 beats/min to 93 ± 9 beats/min ($p < 0.02$), an acceleration not observed with captopril (80 ± 10 to 82 ± 11 beats/min) (Table II).

Correlations: Whatever the conditions attending measurement of plasma renin activity, the latter never correlated with plasma volume, the drop in blood pressure after nifedipine or captopril, or the plasma cyclosporine level, neither did blood pressure correlate with renal insufficiency.

Discussion

The present study of 15 hypertensive heart transplant recipients showed that cyclosporine did not stimulate their renin-angiotensin system. This contradicted the results of previous in vitro experiments showing that 8.10^{-6} *M* cyclosporine stimulated renin production by 43% in rat kidney cortex slices[8]; in vivo, 25 or 20 mg/kg of cyclosporine daily also raised plasma renin activity levels in dogs and rats after several days.[7] These results therefore suggested that cyclosporine affects the renin-angiotensin system, and consequently raises

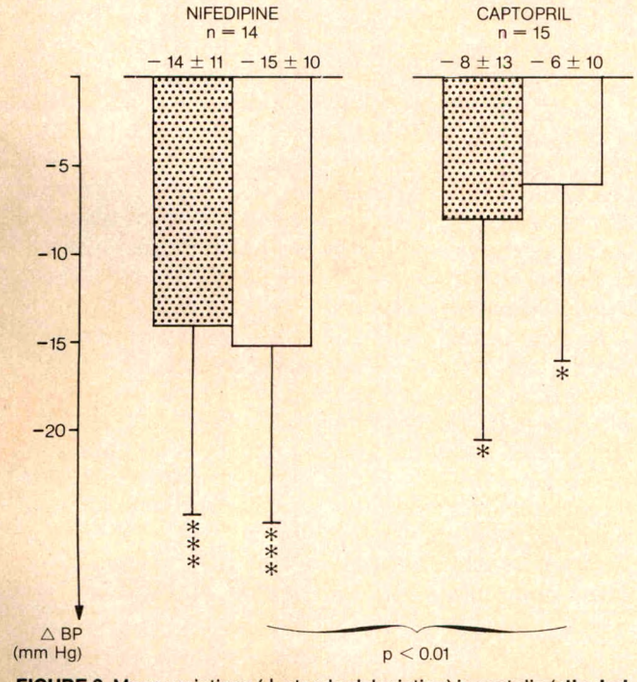

FIGURE 2. Mean variations (± standard deviation) in systolic (**stippled bars**) and diastolic (**clear bars**) blood pressure (BP) recorded 2 hours after 10 mg of nifedipine and 3 hours after 1 mg/kg of captopril, in long-term survivors of cardiac transplantation in whom hypertension subsequently developed. ***$p < 0.005$; *$p < 0.05$.

TABLE I Biochemical Data for Subjects Treated with Cyclosporine and Prednisolone After Cardiac Transplantation

Pt	(Age) (yr)	BP (mm Hg)	Plasma Creatinine (mg/dl) Pre	Plasma Creatinine (mg/dl) Post	Creatinine Clearance (ml/min·1.73 m²)	Plasma Potassium (mmol/liter)	Urinary Sodium (mmol/24 hours)	Urinary Potassium (mmol/24 hours)	Heart Disease Diagnosed
1	57	164/120	1.41	3.33	21	5.1	127	44	NOC
2	51	180/132	1.03	1.24	77	4.1	142	56	CAD
3	50	170/106	1.45	1.64	62	4.9	92	30	NOC
4	49	182/104	1.13	2.43	30	4.6	26	58	NOC
5	46	164/118	2.87	1.41	57	4	20	69	NOC
6	43	190/124	1.93	1.24	77	4.2	171	68	CAD
7	41	140/100	0.60	1.13	107	3.9	55	48	NOC
8	40	162/114	1.36	1.98	28	3.8	104	55	CAD
9	40	170/124	1.34	3.39	81	4	176	56	NOC
10	38	164/132	1.68	2.82	34	4.8	91	53	NOC
11	34	152/102	1.23	2.20	70	4.4	101	42	NOC
12	34	168/102	1.21	4.39	20	4.9	144	56	NOC
13	24	156/110	1.30	1.69	60	5.2	98	81	NOC
14	17	148/90	1.07	1.36	98	4.8	119	62	NOC
15	16	150/100	0.68	1.19	86	4.8	98	46	NOC
Mean	39	164/112	1.35	2.10	61	4.5	104	55	
±SD	±12	±14/13	±0.54	±1*	±28	±0.5	±48	±12	

*$p < 0.05$.
BP = blood pressure; CAD = coronary artery disease; NOC = nonobstructive cardiomyopathy; Post = after cardiac transplantation; Pre = before cardiac transplantation; SD = standard deviation.

TABLE II Variations in Heart Rate and Blood Pressure After Orthostatism and During the Maximal Decrease in Blood Pressure After Ingestion of 10 mg of Nifedipine and 1 mg/kg of Captopril in Long-Term Survivors of Cardiac Transplantation

	Orthostatism (n = 14)					Nifedipine (n = 14)	Captopril (n = 15)
Time (min)*	1	5	10	15	20	46 ± 35	93 ± 34
Heart rate (beats/min)†							
Mean	+6	+8	+9	+13	+10	+10	+2
±SD	±8†	±8‡	±7‡	±9‡	±10‡	±7‡	±6
BP (mm Hg)†							
Mean	−9/0	−7/−1	−8/−2	−10/−4	−10/0	−21/−21	−13/−10
±SD	±12†/±7	±14/±9	±14†/±6	±13‡/±6†	±12‡/±10	±12‖/±14‖	±18†/±17†

* After calcium blocker and converting enzyme inhibition; time on table indicates time (minutes) elapsing before onset of the maximal BP decrease.
† $p < 0.05$; ‡ $p < 0.02$; ‖ < 0.005.
BP = blood pressure; SD = standard deviation.

blood pressure. Here, plasma renin activity values in the recumbent position were within our normal range, and no abnormality was noted after orthostatism. After captopril, which abolished the negative feedback normally exerted by angiotensin II on renin release,[18] there was an increase in plasma renin activity that varied very slightly from patient to patient, and was confirmed by the finding that captopril caused a smaller drop in blood pressure than nifedipine. Our results agree with those of Myers et al,[2] who found no difference in the plasma renin activity levels of cyclosporine-treated patients compared with those of heart transplant recipients treated by conventional therapy. With regard to angiotensinogen, we found normal values, suggesting that prednisolone did not help to generate post-cyclosporine hypertension.[19] Plasma aldosterone values were within our normal range in the supine position, after stimulation by orthostatism and after inhibition by captopril, thus rendering the hypoaldosteronism described by Adu et al[20] unlikely under our conditions. Moreover, none of our patients had hyperkaliemia.

Thompson et al[21] suggested that an aberration in blood pressure control by the central nervous system intervenes in blood pressure regulation, because the heart remains denervated 1 and even 2 years after transplantation.[22] We did not confirm this in our experiments. Urinary excretion of vanilmandelic acid and total metanephrines were in the range of our normal values. The baroreflex regulation of heart rate persisted, since it was raised by both the orthostatic position and by the fall in blood pressure after nifedipine. As is usual in hypertensive patients,[11] the heart rate did not increase after captopril administration. Nifedipine treatment, however, did increase the heart rate in such patients.[10,11] The decrease in blood pressure observed in one of these last studies[10] was roughly similar to that induced by captopril in our patients. Some investigators[23] have attributed the absence of tachycardia after captopril to stimulation of the parasympathetic activity. However, as our patients had a denervated heart which did not respond to atropine,[22] the present results provide reason to believe that stimulation of parasympathetic activity by inhibition of the renin-angiotensin system is not responsible for the absence of tachycardia after captopril.

In conclusion, a state of stimulation of the renin-angiotensin system is improbable in heart transplant patients who become hypertensive. The abnormalities we observed in the laboratory tests of such patients were minor fluid retention (+15%) and renal impairment. Poor adaptation of the renin-angiotensin system to fluid retention may be partly responsible for the increase in the blood pressure in our patients[24]; further investigations are needed before any imbalance between sodium status and renin release can be demonstrated.

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Ventricular Performance in Human Hearts Aged 61 to 73 Years

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The effects of increasing and decreasing cardiac preload by 15% on the left ventricular (LV) performance of 11 carefully screened normal subjects aged 61 to 73 years were examined. Comparisons were made with 11 subjects aged 21 to 28 years. Two-dimensional echocardiograms were obtained before and at the termination of 5 degrees of head-down tilt for 90 minutes and at the termination of graded lower body negative pressure to −40 mm Hg. Heart rates and blood pressures were unchanged after physiologic interventions. Changes in LV end-diastolic and stroke volumes were similar but of a smaller magnitude in the older subjects compared with changes in younger subjects. When LV end-diastolic volumes obtained at each extreme of preload variation were compared, the range of mean change was less in the older (23 ml, 26%) than in the younger subjects (31 ml, 41%). Control LV end-diastolic and end-systolic volumes were greater in the older subjects. This study shows that despite larger control LV volumes, alterations in preload produce changes in the LV end-diastolic and stroke volumes of these older subjects that conform to the normal LV function curve, but that these responses are diminished compared with changes in younger subjects, suggesting an age-related change in diastolic stiffness.

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Both experimental and human studies have shown that aging of the heart produces characteristic changes in different parts of the cardiac cycle.[1–8] Experimental studies of senescent myocardium have shown differing findings regarding both systolic and diastolic stiffness,[1–4] although prolonged contraction duration[3–6] and attenuated inotropic responses to catecholamines[6–8] are consistent findings. Human studies have also produced differing conclusions in older subjects both at rest and during dynamic exercise.[9–11] These differences may be partially attributed to the difficulty in identifying an elderly population that is free of significant intrinsic cardiac disease and, in particular, coronary artery disease.[11]

Recent noninvasive studies in our laboratory have defined the extreme ranges of the relation between left ventricular (LV) end-diastolic and stroke volumes (i.e., the Frank-Starling curve) in normal young subjects and in certain subsets of patients.[12,13] This study examines the effects of large variations in cardiac filling volume on the LV performance of a group of elderly subjects screened to exclude as comprehensively as possible the presence of intrinsic cardiac disease and, in particular, coronary artery disease. Comparisons were made with normal young subjects to define the differences, if any, in the response of the aging left ventricle to large variations in preload.

Methods

Subjects: Studies were carried out in 11 volunteer subjects, aged 61 to 73 years, who were screened to exclude as comprehensively as possible intrinsic cardiac disease. The screening procedure was as follows: Asymptomatic persons from area-aged programs were recruited. Those with a negative history, normal results on physical examination, and normal electrocardiographic findings at rest underwent serial test evaluations to exclude the existence of coronary artery disease by Bayesian analysis.[14] The reported prevalence of coronary artery disease in this asymptomatic age group ranges from 11 to 81%.[15] Data from our laboratory and other laboratories show maximal stress testing to have a sensitivity of 71% and a specificity of 92% for the diagnosis of coronary ar-

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TABLE I Rest Heart Rates, Arterial Pressures, End-Systolic Wall Stress and End-Systolic Stress/Length Ratios in Young and Old Subjects

	Subjects		
	Young	Old	p
Heart rate (beats/min)	56 ± 3	59 ± 1	NS
Blood pressure (mm Hg)			
Systolic	108 ± 3	126 ± 4	<0.005
Mean	79 ± 2	94 ± 3	<0.005
Diastolic	65 ± 2	75 ± 3	<0.02
Wall stress (dynes/cm^2)	68 ± 5	78 ± 6	NS
Stress/length ratio	22 ± 1	24 ± 2	NS

All values are expressed as mean ± standard error of the mean.
NS = not significant.

tery disease.[16,17] After a stress test showing negative results in these subjects, the probability of the existence of coronary disease decreases to 4 to 57%. Bartel et al[18] reported that fluoroscopically detected coronary artery calcification has a sensitivity of 56% and a specificity of 97% for the diagnosis of coronary artery disease. In subjects with a negative result on fluoroscopy after a negative stress test result, the likelihood of the existence of coronary artery disease decreases again to 2 to 37%. While not eliminating the likelihood of the existence of coronary disease, this is an acceptable minimal range of prevalence for the disease. Furthermore, evaluation by 2-dimensional echocardiography of LV segmental wall motion as reported by our laboratory was also carried out.[19] The 11 subjects had no echocardiographic evidence of segmental wall motion abnormalities at rest or during the interventions of head-down tilt and lower body negative pressure.

Eleven subjects, aged 21 to 28 years, were studied for comparison. Details of the study were explained to each of the elderly and young subjects and they gave informed written consent.

Echocardiograms: The echocardiographic techniques and the methods and accuracy of measurements used in our laboratory have been described in detail.[13] Other echocardiographic measurements used in this study were meridional LV wall stress, where wall stress = systolic pressure × end-systolic diameter (ESD)/4 × wall thickness (1 + wall thickness/ESD) dynes/cm^2,[20] and systolic stress-dimension ratio, expressed as meridional wall stress/ESD ratio.[21]

The heart rate was determined from simultaneous electrocardiographic recordings. Blood pressure was recorded at 1-minute intervals throughout each intervention by Narco Bio-Systems programmed electrosphygmomanometer and recorded on a strip-chart recorder. Previous studies have demonstrated good agreement between these studies and auscultatory readings.[12,22] Mean arterial pressure was calculated as diastolic pressure + one-third of the pulse pressure.

Experimental protocol: The protocol of head-down tilt and graded lower body negative pressure used to increase and decrease LV preload has been described in detail.[13] Measurements from echocardiograms obtained before and at the termination of each preload variation were compared. Five degrees head-down tilt for 90 minutes produces a transient increase in central venous pressure of 2.5 cm H_2O, with a return to baseline when the left ventricle reaches its maximal size.[22] Graded lower body negative pressure to −40 mm Hg produces venous pooling with a progressive increase in leg volume of 500 to 700 ml and a transient decrease in central venous pressure of 5 cm H_2O.[22]

On a separate occasion, 6 of the older subjects underwent 5 degrees of head-down tilt for 6 hours to determine whether the time sequence of the response of the older left ventricle to prolonged head-down tilt was different in younger subjects. Leg volumes were estimated before and after 6 hours of tilt and calculated by Simpson's rule from measurements of leg circumferences at 12 well-defined points.[22]

Values determined before and at the termination of each intervention were compared and significant differences were determined by analysis of variance for single factor experiments having repeated measures.[23] When significant differences ($p < 0.05$) between groups were found, within-group differences were determined by the Student-Newman-Keuls multiple range test and values <0.05 were considered significant. Power curves and linear regression equations were determined from individual values of stroke volumes and end-diastolic volumes to obtain LV function curves.

Results

Rest heart rates, systemic arterial pressures, end-systolic wall stress and end-systolic stress/length ratios are listed in Table I. The anticipated differences in arterial pressures associated with age were found. No significant differences were found between the young and the older subjects in rest heart rate, end-systolic wall stress and end-systolic stress/length ratio. Changes in LV dimensions, shortening fraction, mean velocity of circumferential fiber shortening, heart rate and blood pressure are summarized in Table II. There were no significant differences between control data in either subject group before head-down tilt and before lower body negative pressure.

In the young subjects, the changes after both head-down tilt and lower body negative pressure were identical to those found previously in our laboratory (Table II, Fig. 1). Significant changes included an 18% increase in end-diastolic volume and a 31% increase in stroke volume during head-down tilt, and a 16% decrease in end-diastolic volume and 22% decrease in stroke volume during lower body negative pressure (Fig. 2).

In the older subjects during head-down tilt, mean end-diastolic volume increased 8%, from 104 ± 9 to 112 ± 9 ml ($p < 0.001$) and mean stroke volume increased 13%, from 58 ± 6 to 65 ± 7 ml ($p < 0.01$) (Fig. 1 and 2). Mean end-diastolic diameter increased from 4.7 ± 0.2 to 4.8 ± 0.2 cm and mean ESD decreased from 3.3 ± 0.2 to 3.1 ± 0.3 cm. End-systolic volume, ejection fraction, mean velocity of circumferential fiber shortening, heart rate and blood pressure did not change significantly during head-down tilt (Table I, Fig. 1).

TABLE II Effects of Head-Down Tilt and Lower Body Negative Pressure on Young and Old Subjects

	Young Subjects				Old Subjects			
	Head-Down Tilt		LBNP		Head-Down Tilt		LBNP	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
EDD (cm)	4.5 ± 0.1	4.8 ± 0.1	4.5 ± 0.1	4.2 ± 0.1	4.7 ± 0.2	4.8 ± 0.2	4.7 ± 0.2	4.4 ± 0.2
ESD (cm)	3.2 ± 0.1	3.3 ± 0.1	3.2 ± 0.1	3.1 ± 0.1	3.3 ± 0.2	3.1 ± 0.3	3.3 ± 0.1	3.2 ± 0.1
SF (%)	0.30 ± 0.02	0.33 ± 0.01	0.30 ± 0.02	0.27 ± 0.01	0.30 ± 02	0.31 ± 0.02	0.30 ± 0.02	0.27 ± 0.01
Mean Vcf (circ/sec)	0.86 ± 0.05	0.91 ± 0.04	0.83 ± 0.05	0.82 ± 0.04	0.83 ± 0.06	0.84 ± 0.05	0.81 ± 0.06	0.78 ± 0.06
HR (beats/min)	56 ± 3	52 ± 3	53 ± 3	60 ± 4	63 ± 2	61 ± 1	59 ± 1	58 ± 4
Systolic BP (mm Hg)	107 ± 3	108 ± 3	107 ± 3	109 ± 4	126 ± 4	130 ± 5	131 ± 4	126 ± 4
Mean BP (mm Hg)	79 ± 2	80 ± 3	79 ± 2	83 ± 3	92 ± 3	94 ± 3	95 ± 3	90 ± 5
Diastolic BP (mm Hg)	65 ± 2	66 ± 3	65 ± 3	69 ± 3	75 ± 2	76 ± 2	77 ± 2	77 ± 2

All values are expressed as mean ± standard error of the mean.
BP = blood pressure; EDD = end-diastolic diameter; ESD = end-systolic diameter; HR = heart rate; LBNP = lower body negative pressure; SF = shortening fraction; Vcf = velocity of circumferential fiber shortening.

In the older subjects, during lower body negative pressure, mean end-diastolic volume decreased 15%, from 104 ± 9 to 89 ± 8 ml ($p < 0.001$) and mean stroke volume decreased 20%, from 59 ± 6 to 48 ± 5 ml ($p < 0.001$) (Fig. 1 and 2). Mean end-diastolic diameter decreased from 4.7 ± 0.2 to 4.4 ± 0.2 cm and mean end systolic diameter from 3.3 ± 0.1 to 3.2 ± 0.1 cm. End-systolic volume, ejection fraction, mean velocity of circumferential fiber shortening, heart rate and blood pressure did not change significantly during lower body negative pressure (Table I, Fig. 1).

When end-diastolic volumes obtained at each extreme of preload variation during head-down tilt and lower body negative pressure were compared, the range of mean change was less in the older than in the younger subjects. In the young subjects, the range in mean end-diastolic volume of 32 ml represented a range of change of 34% of the control end-diastolic volume at rest, and a 41% increase from the end-diastolic volume during lower body negative pressure. In the older subjects, the change in mean end-diastolic volume of 23 ml represented a range of change of 23% of the control end-diastolic volume at rest and a 26% increase from the end-diastolic volume during lower body negative pressure.

Individual data relating stroke volume to end-diastolic volume at rest and during both interventions in both subject groups are shown in Figure 3. In the young subjects, the data are consistent with previous reports from our laboratory, conforming to a normal LV function curve, best described by the power curve stroke volume equaling 0.83 end-diastolic volume$^{0.9}$ ($r = 0.87$, $p < 0.001$); this is not significantly different from the linear regression stroke volume equaling 0.6 end-diastolic volume + 0.9 ($r = 0.88$, $p < 0.001$). In the older subjects, the data conformed to a similar LV function curve best described by the power curve stroke volume equaling 0.58 end-diastolic volume$^{0.99}$ ($r = 0.88$, $p < 0.001$); this is not significantly different from the linear regression stroke volume equaling 0.6 end-diastolic volume + 3.9 ($p < 0.001$).

The changes in LV dimensions and leg volumes in the 6 older subjects who underwent head-down tilt for a prolonged period of 6 hours on a separate occasion are illustrated in Figure 4. The maximal increase in mean end-diastolic and stroke volumes were of the same magnitude as the previous study of 11 older subjects and occurred after 90 minutes, without further increase during the subsequent 4½ hours. Leg volume decreased from 7.4 ± 0.2 to 7.0 + 0.2 liters ($p < 0.05$), corresponding to a combined volume change (both legs) of 0.8 liter.

Discussion

This study shows that in normal older subjects, the response of the left ventricle to increases and decreases in preload of 15% produces changes that conform to a normal ascending LV function curve, but which are diminished when compared with changes in normal young subjects. When end-diastolic volumes obtained at each extreme of preload variation were compared, the elderly subjects had an increase of only 26% of their lowest end-diastolic volume during lower body negative pressure, whereas the young subjects had an increase

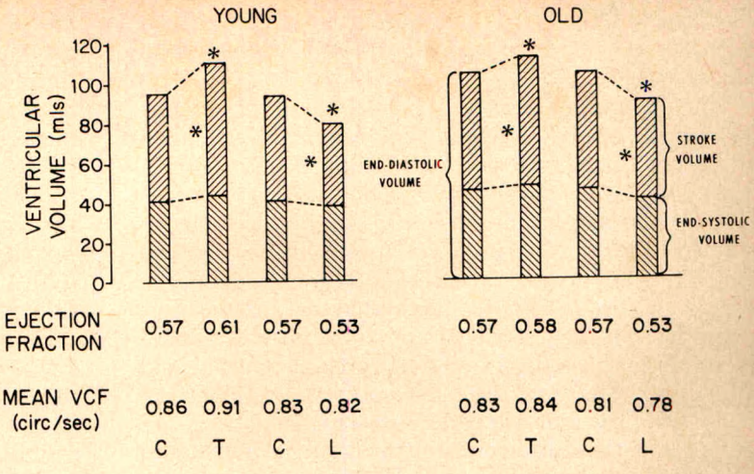

FIGURE 1. Changes in left ventricular end-diastolic, end-systolic and stroke volumes, and ejection fraction and mean velocity of circumferential fiber shortening (VCF) from control values (C) during head-down tilt (T) and lower body negative pressure (L) in young and old subjects. **Asterisks** represent significant changes in mean values. Circ = circumference.

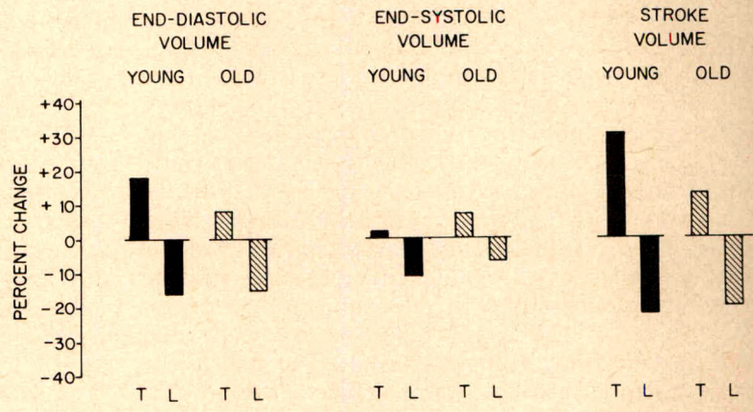

FIGURE 2. Percent changes in left ventricular end-diastolic, end-systolic and stroke volumes from control values during head-down tilt (T) and lower body negative pressure (L) in young and old subjects.

of 41%. Furthermore, the end-diastolic and stroke volumes of the older subjects ranged over a series of higher points on the normal Frank-Starling curve, despite body weights equivalent to those of the young subjects.

Previous studies carried out to determine the effect of age on the hemodynamic responses to various physiologic interventions have shown an attenuated heart rate and blood pressure response to head-up tilt, the Valsalva maneuver, the cold pressor test and static exercise.[24] A possible explanation for these altered responses was a reduction in baroreceptor activity with age as previously shown by Gribbin et al.[25] However, in our studies, no significant changes in heart rate or blood pressure occurred during either head-down tilt or lower body negative pressure.

These findings concur with those of Ebert et al,[26] who showed no changes in heart rate or blood pressure in subjects aged 50 to 59 years during graded lower body negative pressure to −40 mm Hg. Furthermore, they demonstrated a significant reduction in stroke volume during lower body negative pressure in their subjects compared with those of a young group of subjects. These

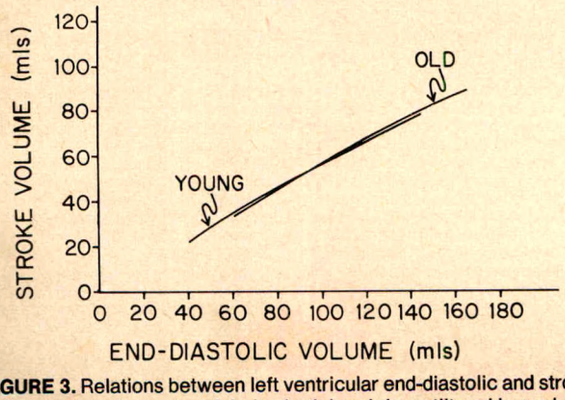

FIGURE 3. Relations between left ventricular end-diastolic and stroke volumes at supine rest and during both head-down tilt and lower body negative pressure in young and old subjects.

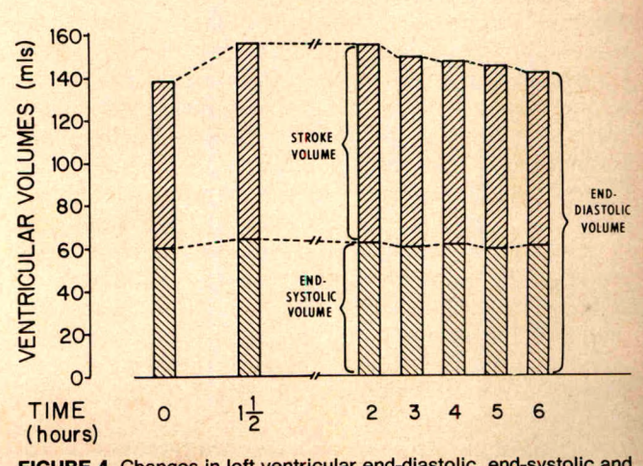

FIGURE 4. Changes in left ventricular end-diastolic, end-systolic and stroke volume from control values (time 0) during 6 hours of head-down tilt in 6 of the elderly subjects.

findings, obtained by impedance cardiography, concur with our echocardiographically estimated changes in stroke volume.

The findings in our study have several possible explanations, although some questions remain. Although it has been suggested that older subjects have less venous compliance changes during physiologic interventions,[24] the magnitude of central fluid shift demonstrated by a reduction in leg volume of a mean of 800 ml is identical to the magnitude found in younger subjects. This would appear to confirm that no comparative difference in magnitude of central fluid shift was a factor. It has been suggested that a greater central blood volume may exist in the older subjects.[27] Higher LV end-diastolic volumes at rest in our older subjects would comparative measurements of transthoracic impedance in young and older subjects by Ebert et al[26] showed no differences, suggesting that increased central blood volume is unlikely. The older human left ventricle may operate near its maximal volume, as suggested by Parker and Case.[28] They summarized several of their studies during various interventions with changes in blood volume and filling pressures and concluded that the human LV function curve reaches a plateau rapidly after relatively small increases in end-diastolic volume. Previous studies in normal young subjects in our laboratory do not support this concept having findings similar to those of the young subjects in this study.[12] Apparently, our findings in older subjects do not concur with this concept either. Figure 3 shows that while the range of changes in end-diastolic and stroke volumes is less than in the young subjects, the proportional changes in stroke volume with changes in end-diastolic volume are identical, without movement off the normal Frank-Starling curve. Furthermore, there is no evidence that the plateau phase of the curve has been reached in these older subjects.

The value of echocardiography in serially evaluating changes in LV performance during acute interventions is well accepted. The calculation of LV volumes is based on the assumption that the left ventricle is always ellipsoid in shape and the minor diameter is always half the major diameter.[12] At the extremes of ventricular volumes encountered in our subjects, the ventricle may have altered its shape, becoming more ellipsoid at small volumes and more spherical at higher volumes. The regression equation of Teichholz et al[29] was derived from a series of angiographically normal ventricles over a wide range of volumes than those encountered in our patients during the various interventions. Furthermore, estimations of ventricular volumes in all types of cardiac disease by 2-dimensional echocardiography have shown a better correlation with angiography.[30] However, the linear dimensional changes are identical to the volume changes, the regression equation used is valid over the ranges of ventricular volumes of our subjects, and evidence of the existence of coronary disease excluded subjects from the study. Thus, an intrinsic error in volume estimation would apply consistently to comparative values.

Considerable effort was made in this study to select older subjects for study who were free of significant intrinsic cardiac disease and, in particular, coronary artery disease. The use of serial test evaluations to determine prevalence of disease and, in particular, coronary artery disease, has been advocated as acceptable in a normal population, in which cardiac catheterization cannot be justified.[14] The screening procedure used for providing the subjects in our study was more thorough than some[10] and less thorough than others.[11] Without cardiac catheterization, however, the presence of coronary artery disease cannot be ruled out. Nevertheless, the selection of 11 subjects older than age 60 years, with a less than 2 to 37% likelihood of having coronary artery disease, and who had no echocardiographic evidence of segmental wall motion abnormalities at rest or during the interventions, appear to make up a suitable subset of subjects for study.

The differences in mean arterial pressures between the young and older subjects may serve to explain the differences in ventricular dimensions in the 2 groups. Should this be the case, one would expect significant differences in both end-systolic wall stress and the stress/length ratio between the 2 groups. Furthermore, there were no differences in mean heart rate between the 2 groups of subjects, either at rest or during the interventions of head-down tilt and lower body negative pressure.

Acknowledgment: We are grateful to Arvella Peters for her technical assistance and to Reba Beaty for her secretarial help.

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Magnetic Resonance Imaging in Pulmonary Arterial Hypertension

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Magnetic resonance imaging (MRI) was used to examine the right ventricle and pulmonary arteries in 17 patients with pulmonary artery (PA) hypertension documented by cardiac catheterization. The study population consisted of 7 patients with primary pulmonary hypertension, 7 with Eisenmenger's syndrome and 3 with pulmonary hypertension secondary to lung disease. The MRI studies of patients were compared with those of 10 normal volunteers. Multislice gated transaxial images encompassed the right ventricle and central pulmonary arteries, showing the severity of right ventricular (RV) hypertrophy in proportion to the elevation of PA pressure and reversal of septal curvature when PA pressure approximated systemic pressure. End-diastolic RV wall thickness and mean pulmonary pressure correlated well (r = 0.79). MRI showed enlargement of PAs in all patients with PA hypertension. A magnetic resonance signal was present in the PAs throughout the cardiac cycle in patients with severe PA hypertension (more than 90 mm Hg) and was absent during systole in normal subjects. A signal within the PAs in systole is consistent with decreased flow velocity in patients with severe PA hypertension. MRI was useful in detecting each of the congenital anatomic defects in patients with Eisenmenger's syndrome.

This study indicates the potential of MRI for evaluating the severity of PA hypertension by providing direct measurements of RV wall thickness and PA diameter and by detecting abnormal intraluminal signal intensity during the cardiac cycle.

(Am J Cardiol 1985;56:938–942)

Magnetic resonance imaging (MRI) has emerged as a noninvasive method for visualization of cardiac structures.[1,2] Because MRI displays the blood pool as very low or no signal intensity with the spin echo technique, the walls of blood vessels and cardiac chambers are visualized without contrast medium.

This study was undertaken to evaluate the capability of MRI to define the anatomic features and origin of pulmonary artery (PA) hypertension and to assess the severity of PA hypertension.

Methods

Study population: The study population comprised 10 normal men, aged 28 to 44 years, and 17 patients with PA hypertension. The latter patients underwent cardiac catheterization before MRI study. Seven patients had primary PA hypertension. The 10 patients with secondary PA hypertension included 3 with a variety of parenchymal lung diseases (obstructive and interstitial) diagnosed on chest radiograph and pulmonary function tests and 7 with Eisenmenger's syndrome documented by the demonstration of congenital heart disease at angiography. The clinical and hemodynamic findings are given in Table I.

Magnetic resonance technique: The magnetic resonance imager for this study used a superconducting magnet operating at a field strength of 0.35 tesla and a resonance frequency for hydrogen of 15 MHz. This imager has been described in detail.[3] A multiplane selective irradiation technique was used for data acquisition and sectional (plane) images were reconstructed by the 2-dimensional Fourier transform technique. The slices were 7 mm thick. The reconstruction matrix was 256 horizontal and 128 vertical lines.

The imaging sequence was spin echo with echo delay times of 28 and 56 ms. First and second spin echo images were acquired at 5 adjacent anatomic levels during each acquisition. The repetition rate, or interval between sets of radiofrequency pulses, was determined by each subject's heart rate. In all subjects images gated to every heart beat were obtained. The gating system has been described.[4]

Data analysis: Ten to 15 adjacent transverse tomographic images were recorded in all subjects; these images extended through the level of the main PA and its bifurcation and through the heart (from the great vessels to the apex). Five adjacent sagittal images were obtained in 2 patients with Eisenmenger's disease. Images were analyzed to determine the presence and location of structural abnormalities (Table I). The septal curvature was described as convex, straight or concave toward the right ventricle.

The ventricular wall thicknesses were determined at end diastole (5 ms after the R wave of the electrocardiogram). A calibrated grid was available for superimposition on the images. The anterior wall of the right ventricle, septum and posterior wall of the left ventricle were measured along a line through the middle of each ventricle and perpendicular to the septum. A detailed description of the site and method for mensuration for MRI studies is available.[5] The septal thickness could not be determined in 2 patients with Eisenmenger's disease because of the presence of large ventricular septal defects. The main pulmonary trunk was measured in systole,

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TABLE I Clinical, Hemodynamic and Magnetic Resonance Imaging Features

Pt	Age (yr) & Sex	Dx	Pulmonary Pressure (mm Hg)		MRI Measurements	
			Systolic	Mean	MPA Diameter (Systolic) (cm)	RV WT (Diastolic) (cm)
1	42F	PPH	120	82	3	1.0
2	34M	PPH	163	102	4	2.0
3	48F	PPH	88	52	4	1.0
4	15F	PPH	191	120	3.2	1.2
5	24F	PPH	131	74	3.5	1.4
6	28F	PPH	115	69	3.5	0.8
7	31F	PPH	81	55	3.2	0.5
8	55M	LD	51	37	3.8	0.5
9	43M	LD	68	45	. . .	0.6
10	59F	LD	54	37	3.6	0.5
11	47F	PDA	118	76	4	0.7
12	36F	ASD	130	97	4	1.5
13	39F	ASD	94	76	3	1.0
14	35M	VSD	130	79	4	1.6
15	52M	VSD	155	118	4	2.0
16	32M	TG,VSD	95 (95)	72 (72)	5	1.3
17	33F	DORV,VSD	96 (95)	72 (65)	3	1.0

Values in parentheses are systolic blood pressure values.
ASD = atrial septal defect; DORV = double outlet right ventricle; Dx = diagnosis; LD = lung disease; MPA = main pulmonary artery; MRI = magnetic resonance imaging; PDA = patent ductus arteriosus; PPH = primary pulmonary hypertension; RVWT = right ventricular wall thickness; TGV = transposition of the great vessels; VSD = ventricular septal defect.

on the transverse slice 1 cm caudal to the origin of the right PA. The ratio of the diameter of the PA to that of the aorta was determined at this same level. The ratio of the left descending PA to the descending aorta was taken at a more caudal level.

The magnetic resonance signal within the lumen of the PAs was determined on each of 5 images obtained during a single imaging period. These 5 multislice images corresponded to 5 phases of the cardiac cycle: end diastole; end diastole + 100 ms; end diastole + 200 ms; end diastole + 300 ms; and end diastole + 400 ms. Each of the images were examined for magnetic resonance signal within the lumen of the central PAs. The images extending up to 300 ms after end diastole occurred within the systolic phases of the cardiac cycle.

The presence of signal in the PAs was graded from 1 to 5 by the following criteria: 1/5 for PA signal present only on the image at end diastole and 2/5 for signal present on 2 images, and so forth, up to 5/5 for signal present on all 5 images. This determination was made on the second spin echo image (TE = 56 ms) because this image is more sensitive for intraluminal flow signal[1,2]; the assessment was made in the center of the PA lumen. All observations and measurements were made by 2 independent observers without knowledge of the results of the catheterization.

Statistical analysis was performed using standard linear regression and one way analysis of variance. Mean values and standard deviation are provided for all measurements.

Results

Normal findings: The transverse images at the level of the great vessels showed normal position and size of the ascending aorta and the main pulmonary trunk and its branches (Fig. 1). The diameters and the relation between these vessels are shown in Table II.

Transverse images taken from the same level but at different times during the cardiac cycle demonstrated a magnetic resonance signal in the PAs and aorta only on the end-diastolic image. During systole there was no signal within the lumens of the aorta or the PAs (Fig. 1).

In Figure 2 (left) normal cardiac chambers are shown. The septum has a crescent shape, with its convexity toward the right ventricle. Normal wall thickness measurements are listed in Table II.

Anatomic findings in patients with pulmonary hypertension: The main PA was enlarged in every patient with PA hypertension (Table I). The ratio of the diameter of the main pulmonary trunk to that of the ascending aorta and the ratio of the diameter of the left descending PA to that of the descending aorta were increased in all patients with elevated PA pressure (Table II). The magnetic resonance signal within the pulmonary artery (Fig. 3) was present in systole in all but 1 patient with primary PA hypertension and all but 1 patient with Eisenmenger's syndrome. This is in contradistinction to the absence of intraluminal signal in the ascending and descending aorta during systole.

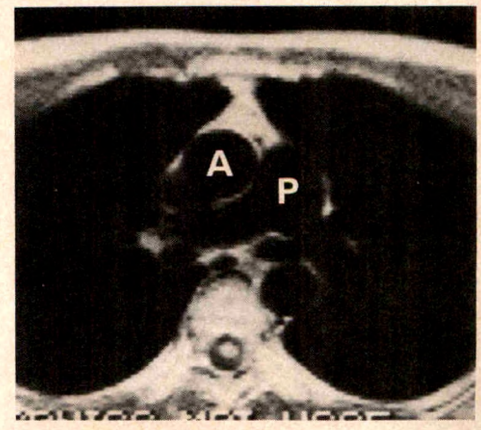

FIGURE 1. Transverse images at the level of great vessels in a normal patient. Image was acquired in systole. During systole there is absence of a magnetic resonance signal, indicating normal flow. A = ascending aorta; P = main pulmonary artery.

TABLE II Pulmonary Artery and Right Ventricular Dimensions as Measured by Magnetic Resonance Imaging

	Normals	1° PAH	2° PAH (LD)	2° PAH (Eisenmenger)	p Value
Main PAD (cm)	2.5 ± 0.4	3.9 ± 0.5*	3.6 ± 0.5*	3.7 ± 0.5*	0.05
Main PA/asc. aorta	0.9 ± 0.2	1.4 ± 0.2*	1.1 ± 0.1	1.4 ± 0.3*	0.05
Desc. LPA/desc. aorta	0.4 ± 0.1	1.1 ± 0.3*	0.8 ± 0.1*	1.0 ± 0.2*	0.01
RVWT (cm)	0.3 ± 0.1	1.2 ± 0.4*	0.6 ± 0.1	1.3 ± 0.3*	0.01
SWT (cm)	1.0 ± 0.1	1.2 ± 0.3*	1.2 ± 0.3	1.3 ± 0.5	0.05
PWT (cm)	1.0 ± 0.1	1.1 ± 0.2	0.9 ± 0.1	1.0 ± 0.3	NS

* Significant difference compared with values in normal subjects.
Values are mean ± standard deviation.
Asc. = ascending; Desc. = descending; Desc. LPA = descending left pulmonary artery; NS = not significant; PA = pulmonary artery; PAD = PA diameter; 1° and 2° PAH = primary and secondary pulmonary hypertension; PWT = posterior wall thickness of the left ventricle; RVWT = right ventricular wall thickness; SWT = septal wall thickness.

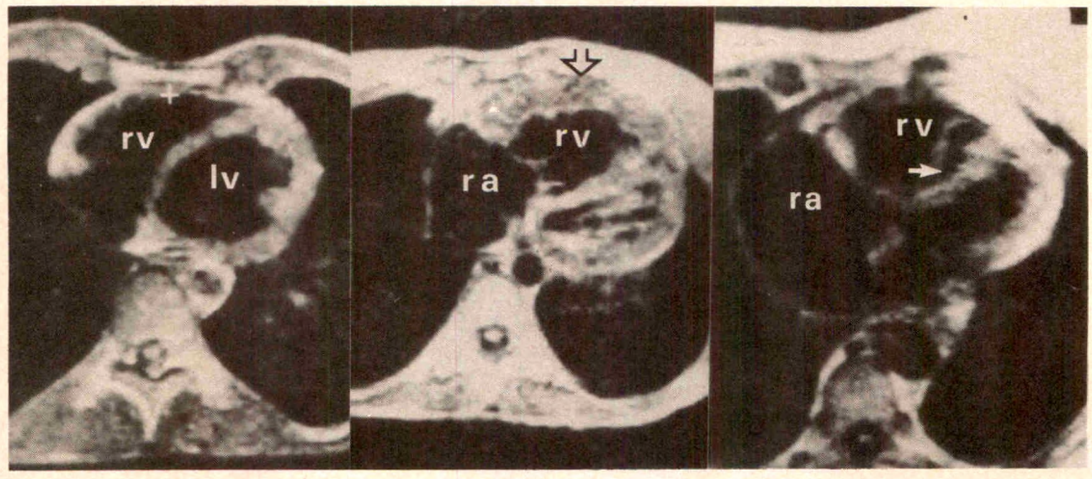

FIGURE 2. Transverse images at the level of the ventricle. **Left,** normal heart indicating where the anterior wall of the right ventricle (rv) was measured. **Middle,** gated image from a patient with primary pulmonary artery hypertension illustrating the severe hypertrophy of the right ventricular wall (**arrow**) and the straight septum. **Right,** concave septum (**arrow**) and enlarged right ventricle and right atrium (ra). LV = left ventricle.

The thickness of the anterior wall of the right ventricle was increased in direct relation to the severity of the PA systolic pressure (r = 0.76) (Table I, Fig. 2 [middle] and 4 [top]). The septal curvature was frequently altered in patients with PA hypertension; it was either straight or concave toward the right ventricle (Fig. 2). Septal curvature was abnormal in 6 patients with primary PA hypertension and 5 patients with Eisenmenger's syndrome. The right ventricle and right atrium were enlarged in all patients with PA hypertension.

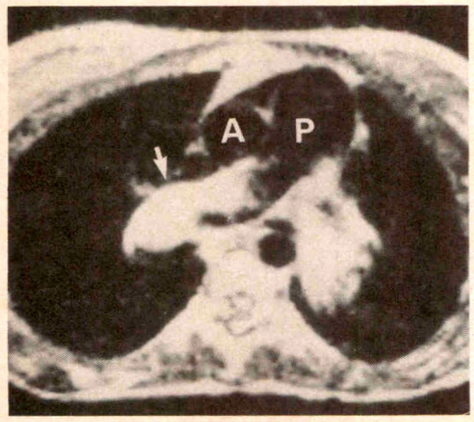

FIGURE 3. Transverse images at the level of great vessels in a patient with primary pulmonary artery hypertension. The main pulmonary artery (P) and its branches are enlarged and show intraluminal signal (**arrow**) during systole. Note the absence of signal in the aorta. A = ascending aorta.

Origin of pulmonary artery hypertension: In patients with Eisenmenger's syndrome, MRI was useful in determining the origin of PA hypertension. MRI detected the anatomic defects in all but 1 patient with Eisenmenger's syndrome. That patient had had a patent ductus arteriosus closed surgically 30 years before the study, and therefore had no anatomic defects other than sequelae of PA hypertension on the right ventricle.

Severity of pulmonary hypertension: As a measure of the severity of PA hypertension, the relation between right ventricular wall thickness and PA systolic pressure was defined (Fig. 4). The equation for the regression line of this relation is:

$$\text{PA systolic pressure (mm Hg)} = 59.2 \times \text{RV wall thickness} - 45.8 \quad (r = 0.76,\ \text{SEE} = 46 \text{ mm Hg},\ n = 17).$$

Figure 4 (bottom) shows the relation between RV wall thickness and mean PA pressure (r = 0.79, SEE = 16

mm Hg, n = 17). The regression equation was:

PA mean (mm Hg) = 10.1 × RV wall thickness + 30.

There was also a significant linear relation between the size of the main PA in systole and PA systolic pressure. The correlation coefficient and the standard error of estimate (SEE) for this relation were 0.76 and 21 mm Hg, respectively. The ratio of the diameter of the main pulmonary trunk to the ascending aorta showed a poorer correlation with systolic PA pressure (r = 0.59, SEE = 32 mm Hg). As another index of severity, we analyzed the septal curvature. When PA systolic pressure was plotted against septal curvature, every patient with pressure greater than 90 mm Hg had either a straight or concave septum (Fig. 5).

In most patients with PA hypertension a magnetic resonance signal was present in the PA throughout systole. When the frequency of intrapulmonary signal at the 5 phases of the cardiac cycle was compared with systolic PA pressure, only 1 patient with a pressure greater than 90 mm Hg showed the normal pattern consisting of intraluminal signal confined only to the end-diastolic image. Only 1 patient with pressure less than 90 mm Hg had pulmonary artery signal on the images obtained during systole (Fig. 6).

Discussion

MRI with electrocardiographic gating defined several characteristic anatomic features in patients with PA hypertension. The main PA was enlarged in all the patients with PA hypertension, including those with mild elevation of PA pressure. In our study population systolic PA pressure and diameter of the main PA correlated well (r = 0.76, SEE = 21 mm Hg, n = 13).

An interesting finding was the presence of PA signal during systole in patients with severe PA hypertension. Generally, blood flowing in a laminar fashion at normal velocity in large blood vessels causes no intraluminal magnetic resonance signal during systole. In this study, none of the normal subjects had magnetic resonance signals in the PAs during systole. In severe PA hypertension, it is expected that blood will be flowing at lower velocity and, consequently, cause intraluminal signal. In fact, 11 of the 12 patients with a systolic PA pressure greater than 90 mm Hg had magnetic resonance signal in their PAs during systole. This low flow situation may be the cause or the result of thrombosis within the PAs. In a recent study[6] lung tissue obtained at autopsy from 56 patients with primary PA hypertension revealed thrombotic material within the PAs in 57% of the

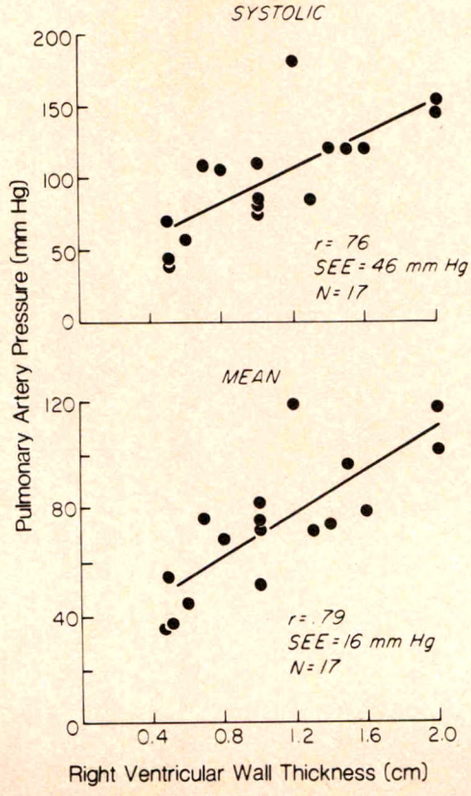

FIGURE 4. Top, relation between systolic pulmonary artery pressure and right ventricular wall thickness. **Bottom,** relation between mean pulmonary artery pressure and diastolic right ventricular wall thickness.

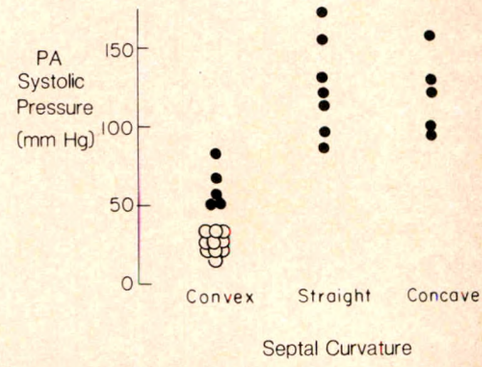

FIGURE 5. Relation between systolic pulmonary artery (PA) pressure and septal curvature. Patients with pressure greater than 90 mm Hg had either a straight or concave septum. **Open circles** represent values from normal volunteers, where pressures were not measured but assumed to be normal on the basis of physical examination.

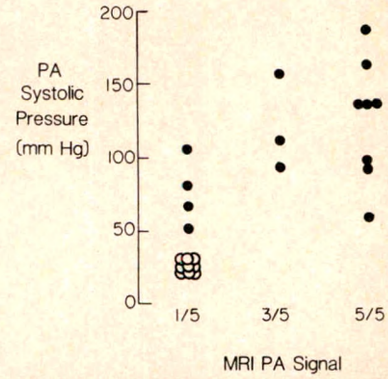

FIGURE 6. Relation between systolic pulmonary artery (PA) pressure and intraluminal signal on magnetic resonance images. 1/5 = signal only during diastole; 3/5 = signal present to midsystole; and 5/5 = signal present throughout systole. **Open circles** as per Figure 4. Only 1 patient with a pressure greater than 90 mm Hg did not have signal during systole and only 1 patient with pressure less than 90 mm Hg had a signal throughout systole. MRI = magnetic resonance imaging.

cases. Consequently, one must differentiate the signal from slow flow from that produced by intraluminal thrombosis. This is usually possible, because thrombus causes intraluminal signal on the first echo image but the signal decreases in intensity on the second echo image. In contrast, slow flow usually produces no signal in the first echo image but substantial signal on the second echo image.[7]

Several investigators[8–12] have used noninvasive methods to predict the PA pressure. Systolic time intervals and the pattern of pulmonic valve motion on M-mode echocardiography have been inconsistent in their accuracy for predicting PA pressure. However, high-quality echocardiographic tracings cannot be recorded in every adult patient, especially in patients with lung disease.[13]

MRI detected a secondary cause of PA hypertension—Eisenmenger's syndrome. Its capability to detect anatomic defects in patients with congenital heart disease was shown in a previous study.[14]

The results of this study suggest that MRI may be a useful noninvasive technique for diagnosing the presence of PA hypertension and assessing its severity. In cases of Eisenmenger's syndrome, MRI detected the anatomic defects in these patients. Consequently, MRI may serve as a noninvasive technique for the diagnostic assessment of patients with suspected PA hypertension and provide insight into the cause and the severity of PA hypertension.

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Early Cardiac Changes Related to Radiation Therapy

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To investigate the incidence and severity of possible radiation-induced cardiac changes, 21 women without heart disease were investigated serially by echocardiography and by measuring systolic time intervals before and up to 6 months after postoperative radiation therapy because of breast cancer. Radiation was associated with a decrease in fractional systolic shortening of the left ventricular (LV) minor-axis diameter, from 0.35 ± 0.05 to 0.32 ± 0.06 ($p < 0.005$), and in the systolic blood pressure/end-systolic diameter ratio, from 4.4 ± 1.2 to 3.9 ± 0.9 mm Hg/mm ($p < 0.005$). The mitral E point-septal separation increased, from 2.8 ± 1.5 to 4.2 ± 2.5 mm ($p < 0.005$). The preejection period/LV ejection time ratio of systolic time intervals increased, but only the decrease within 6 months after therapy was significant ($p < 0.005$). All these changes reflect slight transient depression of LV function, which became normalized within 6 months after therapy. Up to 6 months after therapy, a slight pericardial effusion was found in 33% of the patients. Hence, conventional radiation therapy appeared to cause an acute transient and usually symptomless decrease in LV function, and later, slight pericardial effusion in one-third of the patients. (Am J Cardiol 1985;56:943–946)

Radiation to the mediastinum causes cardiac changes. In autopsies and in clinical studies, fibrosis and thickening of the pericardium has occasionally led to pericardial concretion and tamponade,[1–7] myocardial fibrosis,[1,2,7–10] endocardial fibrosis sometimes causing valve disease,[1–3,7–9] and coronary artery disease owing to coronary artery fibrosis or accelerated atherosclerosis, or both.[1,2,7,10,11] However, most of these studies were performed retrospectively, several years after radiation therapy and usually because of Hodgkin's disease; thus, less information is available concerning acute cardiac changes and their incidence after radiation in humans. The present study investigates noninvasively the possible acute cardiac changes and their incidence during and after postoperative radiation therapy because of breast cancer.

Methods

Patients: Twenty-four consecutive women with breast cancer, treated with radical mastectomy but not with cytotoxic or other drugs, were investigated. Three patients were excluded from the study, 1 because of combined mitral valve disease and 2 because of difficulty in echocardiographic examination. In the remaining 21 women the ages ranged from 31 to 59 years (average 45). No patient had evidence of metastases at the time of the study. One patient had had chest pains 10 years previously when she used contraceptive pills, but no cardiac disease was found and she has since been symptomless. Another patient had occasional palpitations, but all other patients had no cardiac symptoms before radiation therapy. One patient was taking thyroxin substitution therapy because of previous thyroidectomy. Ten patients had undergone left-sided and 11 had undergone right-sided radical mastectomy before the study.

Four patients had slight mitral valve prolapse seen on echocardiography and at clinical investigation. Two patients had slight T inversions in chest leads V_1 and V_2 seen on electrocardiography before radiation. All other patients had normal cardiac status before radiation therapy.

All patients were treated with cobalt-60 gamma radiation from 2 frontal fields: 1 parasternal and 1 neck-axillary, with 10 × 400 rads every other day for 24 days. The operation field was radiated by 250-kV radiographs laterotangentially. The parasternal field was 8 × 16 cm from the upper margin of the sternum (Fig. 1). The radiation dose to the heart was estimated from the isodose curve superimposed on the transversal computerized tomographic picture of the heart (Fig. 2). The maximal dose to the base, right atrium and right ventricle of the heart was about 3,600 rads, and the corresponding cumulative radiation effect 1,467 rets or timedose-fractionation factor 79. The minimal dose to the heart in the radiation field was about 60% of the field dose.

The studies were done before and immediately after completion of the radiation therapy, and 3 and 6 months afterward. The investigation consisted of physical examination, a standard 12-lead electrocardiogram, chest x-ray,[12] measurement of systolic time intervals and echocardiography.

Systolic time intervals were measured with a Hewlett-Packard contact transducer 21050A and a multichannel ultraviolet recorder at a paper speed of 150 mm/s using a standard technique.[14] Measurements were averaged from 10 consecutive cardiac cycles.

Echocardiograms were recorded by the same echocardiographer using a standard echocardiographic technique and patient's position, with ATL Mark III 2-dimensional echocardiographic equipment at a paper speed of 50 mm/s. M-

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mode measurements were made from 5 consecutive cardiac cycles according to the recommendations of the American Society of Echocardiography[13] without knowledge of the chronologic order of the recordings.

Statistical comparisons between different patient groups were made using a Student *t* test. Differences between serial measurements of variables were calculated using nonparametric statistical methods: Friedman's 2-way analysis of variance and Wilcoxon's test.

Results

Symptoms and physical examination: Two patients with pericardial effusion complained of slight exertional dyspnea. One patient had slight exertional dyspnea at 3 months after therapy, but there were no changes in the results of noninvasive study. One patient, in whom there was a slight depression in LV function, complained of dizziness and palpitation after therapy and another patient complained of fatigue 3 months after therapy. The other 16 patients (76%) were symptomless.

No friction rub was heard in patients with pericardial effusion. Diastolic blood pressures were higher in the patients with the right breast removed than in those with the left breast removed before radiation therapy (88 ± 14 vs 75 ± 7 mm Hg, $p < 0.05$) and 6 months after therapy (91 ± 15 vs 77 ± 7 mm Hg, $p < 0.05$). Systolic blood pressure decreased in patients with the right breast removed between the studies before and immediately after therapy, from 141 ± 25 to 127 ± 21 mm Hg ($p < 0.005$), and the difference was still significant between the studies before and 6 months after therapy (141 ± 25 vs 133 ± 26 mm Hg, $p < 0.05$). There were no differences or changes in heart rate except that 3 months after radiation the heart rate was faster in patients with than in those without pericardial effusion (83 ± 9 vs 72 ± 13 beats/min, $p < 0.05$). The blood hemoglobin, packed blood cell volume and serum calcium concentration did not change significantly between studies.

Electrocardiogram and chest x-ray: New electrocardiographic changes after therapy were seen in 4 patients (19%) (Fig. 3): T inversions in 3 and slight ST-segment elevation in 1. In the 3 patients with new electrocardiographic changes, fractional shortening and (in 1) preejection period/LV ejection time ratio (PEP/LVET) were abnormal immediately after radiation therapy and in 1 patient PEP/LVET also at 3 months. The only significant change noted in relative cardiac size measured from chest radiographs[12] was that it decreased in patients whose left breast was removed between the studies immediately after therapy and 3 months later, from 374 ± 55 to 347 ± 48 ml/m^2 ($p < 0.005$).

Echocardiography (Table I): No patients had regional LV wall motion abnormalities during 2 dimensional real-time study. Fractional shortening decreased between the studies before and immediately after radiation therapy (from 0.35 ± 0.05 to 0.32 ± 0.06 [$p < 0.005$]), and mitral valve E point-septal separation (EPSS) increased, respectively (from 2.8 ± 1.5 to 4.2 ± 2.4 mm [$p < 0.005$]) (Fig. 4). Fractional shortening increased again between the studies immediately after therapy and at 6 months, from 0.32 ± 0.06 to 0.35 ± 0.06 ($p < 0.005$). In our laboratory the intraobserver variation

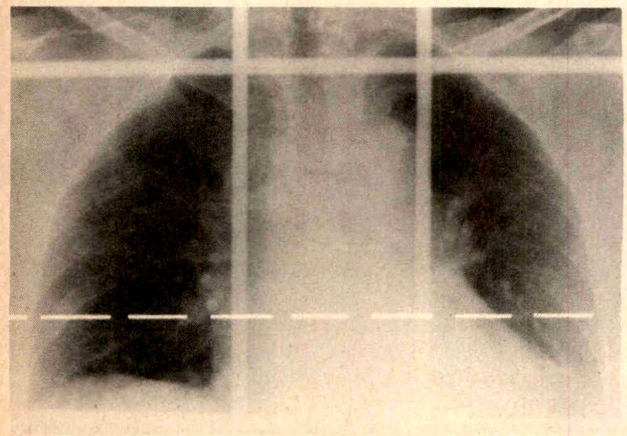

FIGURE 1. Chest radiograph showing the parasternal field of radiation (8 × 16 cm^2). **Dotted line** represents the computerized tomographic plane of Figure 2.

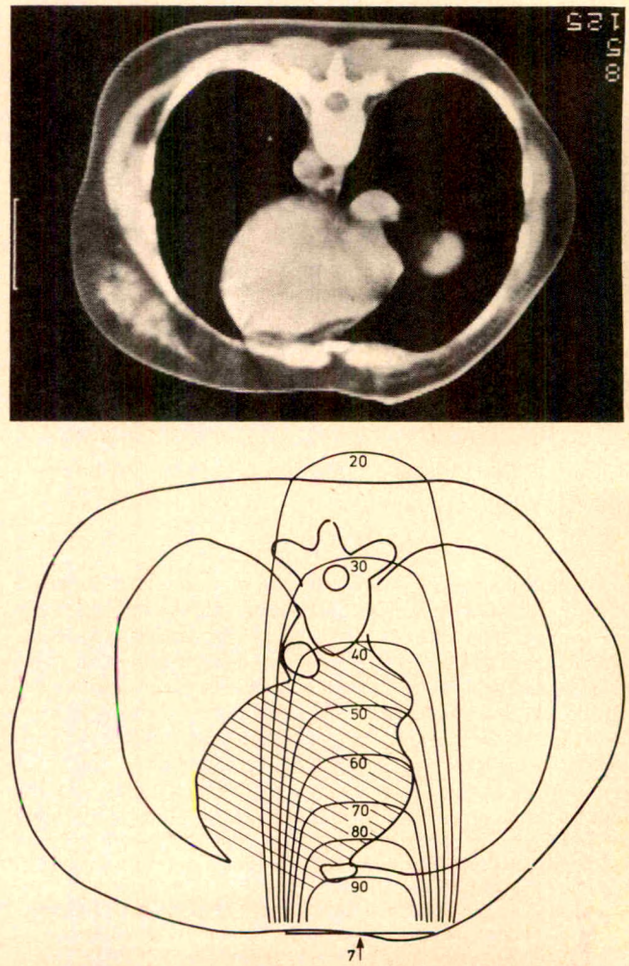

FIGURE 2. Top and **bottom,** transversal computerized tomography plane with isodose curves. **Numbers** represent percentages of the total dose of 4,000 rads.

TABLE I Changes in Echocardiographic Measurements and Systolic Time Intervals

	Left Atrial Diameter (mm)	LV EDD (mm)	LV ESD (mm)	SBP/ESD (mm Hg/mm)	FS	mVCF (circ/s)	EPSS (mm)	PEPI (ms)	LVETI (ms)	PEP/LVET Ratio
Before radiation	33 ± 6	48 ± 5	32 ± 4	4.4 ±1.2	0.35 ± 0.05	1.14 ± 0.22	2.8 ± 1.5	134 ± 13	417 ± 17	0.35 ± 0.05
After radiation	32 ± 5	48 ± 5	32 ± 4	3.9 ±0.9	0.32 ± 0.06	1.07 ± 0.17	4.2 ± 2.5	139 ± 12	412 ± 17	0.38 ± 0.05
3 months later	32 ± 5	47 ± 5	31 ± 4	4.2 ± 1.1	0.34 ± 0.04	1.13 ± 0.17	4.0 ± 1.7	136 ± 14	414 ± 13	0.36 ± 0.06
6 months later	33 ± 6	48 ± 4	31 ± 4	4.3 ± 1.3	0.35 ± 0.06	1.19 ± 0.28	3.9 ± 1.8	132 ± 9	418 ± 15	0.34 ± 0.04

* $p < 0.005$; † $p < 0.05$.
All values are expressed as mean ± standard deviation.
EDD = end-diastolic diameter; EPSS = mitral valve E point-septal separation; ESD = end-systolic diameter; FS = fractional shortening of left ventricular minor axis diameter; LV = left ventricular; LVETI = LV ejection time index; mVCF = mean velocity of LV circumferential fiber shortening; PEPI = preejection period index; PEP/LVET = preejection period/LV ejection time; SBP = systolic blood pressure.

for serial measurements of fractional shortening is 0.02 or less and of EPSS 2 mm or less in patients with normal cardiac size. In 16 patients the decrease of fractional shortening was 0.03 or more and in 8 patients the increase of EPSS was 3 mm or more. If 0.26 is taken as the lower limit of normal fractional shortening, it was found to be abnormal (0.25, 0.17 and 0.22) in 3 patients at the completion of therapy; in all other studies it was within normal limits. The systolic blood pressure/end-systolic diameter ratio decreased between the studies before and immediately after radiation therapy (from 4.4 ± 1.2 to 3.9 ± 0.9 mm Hg/mm [$p < 0.005$]), and increased again between the studies immediately after therapy and at 6 months (from 3.9 ± 0.9 to 4.3 ± 1.3 [$p < 0.005$]). There were no differences in echocardiographic results between patients with the right or left breast removed.

Seven patients (33%) had slight pericardial effusion: one immediately after radiation, one 3 months after and five 6 months after therapy (Fig. 3). There were no differences in results reflecting LV systolic performance between the patients with and those without pericardial effusion, except that changes in the systolic blood pressure/end-systolic diameter ratio were significant in those without than those with pericardial effusion.

Systolic time intervals (Table I): The PEP/LVET ratio increased insignificantly between the studies before and immediately after radiation, but decreased significantly between the studies immediately after radiation and 6 months after therapy, from 0.38 ± 0.05 to 0.34 ± 0.03 ($p < 0.005$) (Fig. 4). If 0.44 is taken as the upper limit of normal,[13] the PEP/LVET ratio was abnormal in 4 patients immediately after radiation and in 2 of these 4 patients 3 months after therapy (Fig. 3). There were no differences in systolic time intervals between patients with and without pericardial effusion, or between patients with the right and those with the left breast removed.

Discussion

Radiation may induce both acute and chronic cardiac changes. After accidental fatal radiation, acute changes include myocardial perivascular edema and hemorrhage, leukocytes scattered in the epicardium and pericardial effusion.[14–16] In therapy, radiation doses may still be enough to cause acute changes in ventricular function. Using echocardiography and measurements of systolic time intervals of the left ventricle, we discovered transient slight depression in LV function related to radiation therapy. Fractional shortening and EPSS[17] correlate fairly well with LV ejection fraction, the latter negatively, when the left ventricle is of normal size and contracts symmetrically, as in our patients. The systolic blood pressure/end-systolic diameter ratio may reflect LV myocardial contractility better than fractional shortening,[18] but because we did not manipulate the afterload, the message of this measurement is lim-

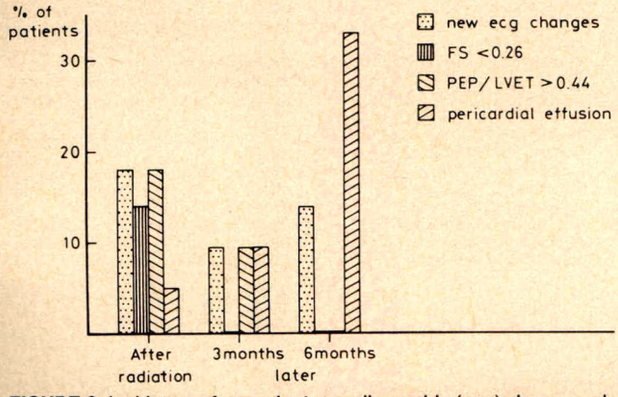

FIGURE 3. Incidence of new electrocardiographic (ecg) changes, abnormal fractional shortening (FS) and preejection period/left ventricular ejection time (PEP/LVET) ratio and pericardial effusion after radiation therapy, expressed as percentages of total number of the patients.

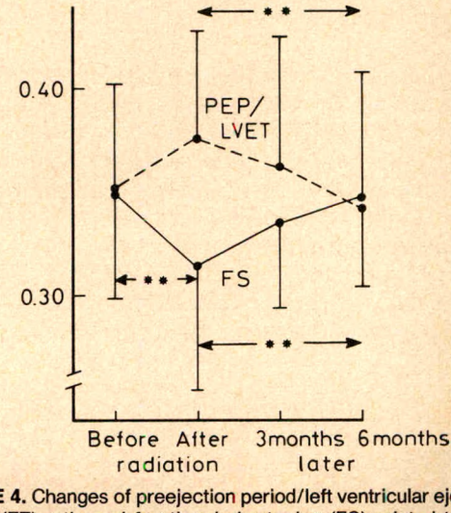

FIGURE 4. Changes of preejection period/left ventricular ejection time (PEP/LVET) ratio and fractional shortening (FS) related to radiation therapy, $p < 0.005$.

ited.[19] Blood pressures were measured from the right arm, so local changes may partially explain changes of blood pressure in patients with the right breast removed. However, the trend in changes of systolic blood pressure/end-systolic diameter ratio was equal in patients with the left breast removed as in the group as a whole.

Fractional shortening and systolic blood pressure/end-systolic diameter ratio decreased, and EPSS increased immediately after radiation therapy; they returned to normal levels within 6 months after radiation. The changes in the PEP/LVET ratio in our patients also reflect transient depression of LV function.[20] Although we did not have a control group who received radiation therapy elsewhere except in the heart, the changes in LV function were obviously caused by the direct effects of radiation in the heart. For instance, a possible peripheral vasodilation or increased sympathetic stimulation would increase and not decrease LV function. Our results are in agreement with those of Arom et al[21] in dogs. After a total dose of 5,000 rads, LV function decreased, expressed as cardiac output and stroke volume at rest and during volume overload. The measurements were lowest at 3 months after therapy and became normal within 7 months.

Only 3 patients had abnormal fractional shortening and 4 had abnormal PEP/LVET ratio after therapy. Although the acute cardiac effects of radiotherapy do not seem to cause clinical symptoms or problems in patients with normal cardiac function, the situation may be different in patients with cardiac failure. Only 1 patient had pericardial effusion immediately after radiation; thus, the acute cardiac effects of radiation appear to be more myocardial than pericardial.

Radiation may also lead to chronic cardiac changes months or usually years after exposure.[1,7,22] In the myocardium there may be fibrosis and in the pericardium thickening and effusion.[2,22–24] Myocardial changes may cause a decrease in LV size, suggesting restrictive cardiomyopathy and a decrease in systolic ventricular function, especially during exercise.[25] According to our results, acute changes in LV function disappear within 6 months after therapy and future control studies will show if LV size or function changes again.

Pericardial effusion was found in 33% of our patients, occurring mostly 6 months after therapy. In earlier studies its incidence has varied from 6 to 30%.[1,4,6,25] For instance, in the study of Applefeld et al[6] the incidence was 11%, but all the patients were symptomatic. Byhardt et al[4] found a 29% incidence of pericardial effusion using measurement of cardiac size from the chest radiographs, of which 86% had effusion within 1 year after therapy. Echocardiography is much more sensitive in detecting pericardial effusion than chest radiography, so the 33% incidence in our patients compares well with other reports. Of the patients with pericardial effusion, only 1 had depression of LV function after therapy (fractional shortening 0.22 and PEP/LVET 0.47), and the measurements reflecting LV function did not change significantly in those with pericardial effusion. Thus, the mechanism by which radiation causes a pericardial reaction may be different from that leading to a myocardial reaction.

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Reproducibility of Left Ventricular Area and Volume Measurements Using a Computer Endocardial Edge-Detection Algorithm in Normal Subjects

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The variability of serially recorded 2-dimensional echocardiograms in normal subjects was determined. During a 2-week period, 10 normal subjects underwent echocardiography 5 times, in 2 laboratories, with use of different ultrasonographs. The video recordings were analyzed using a computer image analysis system (Quantic 1200) to provide standardized left ventricular short-axis areas and area ejection fraction (EF). Left ventricular volumes and volume EF were calculated. The 95% confidence limits of the percent difference for end-diastolic area and volume between 2 samples in a given subject were ±16.8 and ±16.7%, respectively. The limits for end-systolic area and volume were ±15.8 and ±17.0%, respectively. The 95% confidence limits for differences of area and volume EF between 2 recordings were ±12.8 and ±9.7%, respectively. No correlation was found between clinical grade (image quality) and the variability of area measurements. A good correlation (r = 0.98) was found between area and volume EF for any given subject over the 5 observations. These confidence limits are narrower than those previously recorded.

(Am J Cardiol 1985;56:947–952)

Two-dimensional (2-D) echocardiography is a noninvasive method for following changes of left ventricular (LV) function in patients with heart disease. Because no standard exists for accurately calculating LV volume in patients in vivo, definition of the day-to-day variability of 2-D echocardiographic measurements is important. A recent study[1] calculated the 95% confidence limits for percent change of end-diastolic and end-systolic volumes and change in ejection fraction (EF) on serial 2-D echocardiograms. The study group included 20 normal and 10 abnormal hearts. Measurement variability has been noted to be greater in normal than in abnormal hearts using several imaging techniques.[1–3] Thus, the confidence limits established from their mixed population may be narrower than those of a normal population. Also, the LV volumes in the previous study were calculated from manually defined endocardial areas that incorporated a potentially large component of variability related to observer bias and image quality. In the present study normal subjects underwent serial imaging to include the variability expected during routine clinical laboratory 2-D examinations. However, a computer image analysis system (Quantic 1200, Bruce Franklin Inc.) was used to provide LV area measurements. The objective of this study was to quantify the variability of serial measurements of 2-D LV cross-sectional areas and calculated volumes in a normal population using a computer image analysis.

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Methods

Study design: The study group consisted of 10 adult volunteers, 5 men and 5 women, mean age 30 years (range 20 to 49). Entrance criteria were absence of clinical evidence for cardiovascular disease and a 2-D echocardiogram considered adequate for diagnostic purposes in our clinical laboratories. Five subjects underwent imaging with use of a Mark 500 ATL mechanical sector scanner at the Shands Teaching Hospital at the University of Florida, and 5 subjects underwent imaging with an Irex Systems IIIA phased-array scanner at the University Hospital of Jacksonville, Florida. Each subject underwent imaging at approximately the same time of day, in a semirecumbent, left lateral decubitis position, from the same intercostal space and by the same technician. While monitoring a lead II electrocardiogram, recordings were made of the LV midpapillary muscle, the short-axis image having the greatest short-axis diameter and the roundest endocardial

contour (papillary muscles excluded). An apical 4-chamber view was also obtained with the patient in the left lateral decubitus position. This view was recorded with good visualization of the lateral wall endocardium and vertical orientation of the ventricular septum in the field, and when maximal long-axis length and maximal minor-axis dimensions were considered present. Betamax and ½-inch VHS video tape recordings of 10 to 20 cycles were obtained over 9 days on a Monday, Wednesday, Friday, Monday, Wednesday schedule. The previously mentioned internal landmarks and review of previously recorded images of each subject were used by the technicians to match cross-sectional recordings from day to day. Instrument gain was adjusted to the lowest level that provided the most continuous endocardial border while avoiding bloom around endocardial targets and excessive echo dropout.

Image analysis: Images were considered adequate for analysis if approximately 60% or more of the endocardium could be visualized throughout the cardiac cycle. Each recording was graded by 1 observer on a 1+ to 4+ scale to provide an index of image quality. A grade of 1+ indicated that the endocardial borders could be discerned; however, as much as 40% of the endocardial border (not in adjacent quadrants) could be missing during several frames in the cardiac circle. A grade of 2+ indicated that 20 to 30% echo dropout occurred on several frames, and artifact or bloom around the endocardial border provided targets that were not true endocardium and potentially confusing to analysis. A grade of 3+ indicated a study in which the borders were nearly continuous throughout all frames of the cycle. Image dropout (10 to 20%) and artifact were minimal. A grade of 4+ indicated that the borders were continuous with no potentially confusing artifacts.

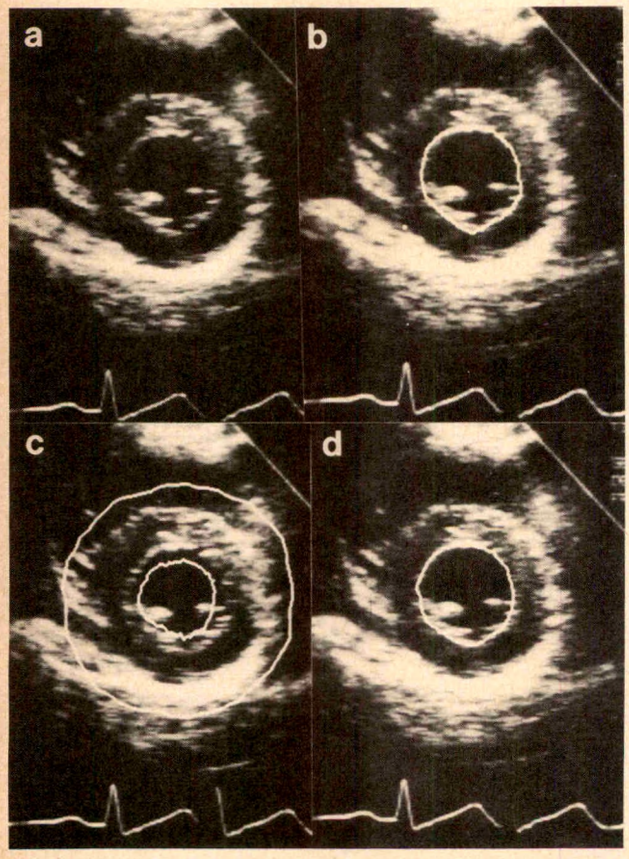


FIGURE 1. Subject 5. An end-systolic video frame showing: **a,** left ventricular short-axis image; **b,** manually traced endocardial border superimposed on the image in panel **a**; **c,** region of search superimposed on the image in panel **a**; **d,** computer-generated endocardial border superimposed on the image in panel **a.**

Cycles were selected randomly for analysis from daily recordings of each subject. The cycles were analyzed using a Quantic 1200 image analysis computer. The first step was the digitization of the selected video images and storage on digital disk. These stored cycles were then redisplayed, allowing the observer to select a single cardiac cycle for image analysis (Fig. 1a). The observer was asked to use a joystick-controlled cursor to calibrate the image using a centimeter scale from the video recording of the echo, and to designate an area of interest to direct the computer search for endocardial echoes. This latter step requires the observer to trace end-diastolic and end-systolic endocardial borders (Fig. 1b). Then, the manually traced end-diastolic border was expanded while the end-systolic border was contracted to provide the computer with a doughnut-shaped region of search (Fig. 1c). The manual tracings were not used in the remainder of the process. On each serial frame, the computer generated a set of borders using image-processing algorithms within the search region. The edge-detection algorithm first seeks endocardial echoes within the designated area by searching outward from the center of the left ventricle in a radial direction along 64 rays. As it searches, it uses an adaptive thresholding technique[4] to identify points where a shift in pixel gray level intensity occurs, consistent with a change in gray level that one would expect it to encounter when moving from LV cavity to myocardium. This set of radial points then provides a rough, static endocardial border. This rough border is modified by the computer using spatial and temporal smoothing algorithms (Fig. 1d). These procedures refine the rough borders by applying constraints to the sequential rough borders (frame to frame) that will conform to the physiologic, temporal and spatial properties of myocardial motion (i.e., the algorithm provides borders limited by the maximal expected distance a true endocardial point can move from frame to frame adjusted for heart rate [Fig. 2]).

The long-axis length was measured by digitizing a point in the center of the mitral valve plane and 1 at the midpoint of the cardiac apex and on end-diastolic and end-systolic frames from 3 consecutive cycles. Long-axis lengths were not available for 3 patients on 1 of the 5 observation days. The computer-generated borders, heart rate, computed end-diastolic and end-systolic areas and the long-axis lengths were stored on floppy disk for subsequent analysis.

Data reduction: The computed areas from 3 cycles recorded on the same day in the same subject were averaged to provide a single end-systolic and end-diastolic area, as well as an area EF observation. Area EF was computed as [(end-diastolic area − end-systolic area)/end-diastolic area] × 100. End-diastolic and end-systolic volumes were calculated as $V = \frac{5}{6}$ AL, where V = volume, A = short-axis area and L = long-axis length. Volume EF was computed as [(end-diastolic volume − end-systolic volume)/end-diastolic volume] × 100. The mean ± standard deviation of the areas, lengths, volumes, and area and volume EF observations for each subject and the group were calculated.

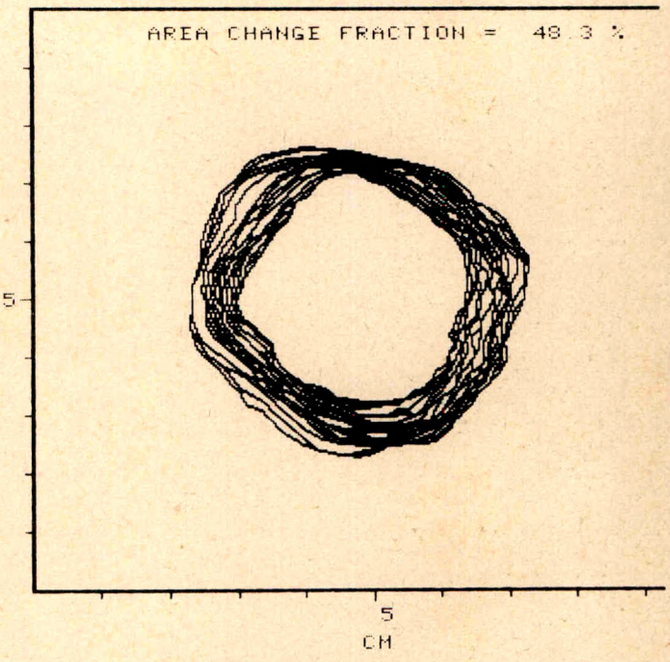
Differences, observed 95th percentile values and correlations: Absolute differences between any 2 end-systolic and end-diastolic areas, volumes, and area and volume EF observations for a subject were calculated. The mean differences were calculated and tabulated for each subject over the 5 observations in the study (Table I). Similarly, percent differences (disregarding sign) between any 2 end-systolic and end-diastolic area and volume measurements for a subject

A

NAME: H. B HOSPITAL:
PATIENT #: 00-000-00 HT: cm WT: kg BSA: m2 AGE:
DIGITIZED BY : DATE: 10/19/84
AREAS AND PERIMETERS - FULL CYCLE 2D SECTOR WALL MOTION ANALYSIS

Frame	Area (cm2)	Perim (cm)
1 ED	19.29	16.05
2	18.73	15.80
3	17.73	15.41
4	16.70	14.93
5	15.22	14.30
6	13.95	13.77
7	12.77	13.10
8	11.62	12.49
9	10.83	12.15
10	10.22	11.81
11 ES	9.98	11.62
12	10.17	11.72
13	10.58	11.98
14	11.69	12.60
15	13.11	13.27
16	14.52	13.88
17	15.59	14.37
18	16.34	14.71
19	16.82	14.99
20	17.06	15.02
21 ED	17.12	15.05

SAMPM VIEW
DIASTOLE AND SYSTOLE BORDERS DISPLAYED



B

NAME: H. B HOSPITAL:
PATIENT #: 00-000-00 HT: cm WT: kg BSA: m2 AGE:
DIGITIZED BY : DATE: 10/19/84
AREAS AND PERIMETERS - FULL CYCLE 2D SECTOR WALL MOTION ANALYSIS

Frame	Area (cm2)	Perim (cm)
1 ED	19.48	16.11
2	18.90	15.76
3	17.92	15.39
4	16.82	14.97
5	15.64	14.42
6	14.45	13.96
7	13.15	13.37
8	12.02	12.80
9	11.01	12.26
10	10.34	11.83
11 ES	9.98	11.61
12	10.07	11.63
13	10.46	11.80
14	11.25	12.17
15	12.44	12.81
16	13.87	13.61
17	15.25	14.25
18	16.15	14.65
19	16.49	14.81
20	16.64	14.86
21 ED	16.75	14.96

SAMPM VIEW
DIASTOLE AND SYSTOLE BORDERS DISPLAYED

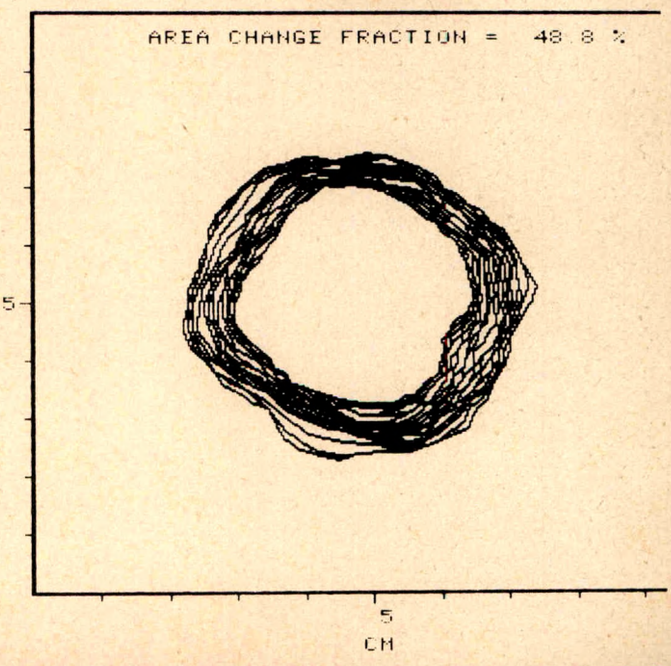


FIGURE 2. A, computer hard-copy output showing short-axis papillary muscle endocardial border measurements of area, perimeter (Perim), and area change fraction for a single cycle in subject 1. **B,** computer hard-copy output of a cardiac cycle recorded during a second sampling period in the same patient. BSA = body surface area; ED = end-diastolic; ES = end-systolic.

TABLE I Clinical Grades, Area, Volume and Ejection Fraction Differences

Sub.	Clinical Grade	End-Diastolic Differences: Area cm²	End-Diastolic Differences: Area %	End-Diastolic Differences: Volume ml	End-Diastolic Differences: Volume %	End-Systolic Differences: Area cm²	End-Systolic Differences: Area %	End-Systolic Differences: Volume ml	End-Systolic Differences: Volume %	Ejection Fraction Differences: Area (%)	Ejection Fraction Differences: Volume (%)
Individual Differences											
1	3.2	0.99	6.1	9.3	8.1	0.49	5.8	3.89	7.3	3.7	3.1
2	2.6	0.77	5.5	6.0	6.4	0.46	7.4	3.96	11.1	3.0	2.9
3	2.6	2.02	13.64	11.3	10.5	0.61	7.5	3.41	6.9	5.8	4.4
4	2.8	0.43	5.2	5.2	5.2	0.43	6.7	3.08	8.3	0.9	1.5
5	3.8	1.97	8.1	13.3	7.6	0.84	8.2	5.66	7.9	4.5	4.4
6	2.0	1.55	8.9	10.3	9.3	0.86	8.2	4.02	7.6	6.0	3.2
7	2.2	1.78	9.9	14.9	10.8	1.14	10.1	4.14	6.1	6.6	4.7
8	1.4	0.89	6.5	6.5	6.3	0.43	5.6	2.52	5.0	4.2	4.0
9	1.6	1.27	8.7	9.1	8.9	0.46	5.6	2.87	5.7	7.2	6.4
10	3.0	0.35	2.2	2.3	1.8	0.65	7.1	4.78	7.2	3.0	4.4
Group Differences											
Mean ±SD		1.23 ±0.58	7.26 ±5.40	7.95 ±4.40	7.31 ±5.30	0.64 ±0.24	7.11 ±4.80	3.83 ±0.93	7.47 ±5.15	4.63 ±1.87	3.89 ±3.19

SD = standard deviation; Sub. = subject.

were calculated. All within-subject area and volume percent differences and area and volume EF differences were sorted by computer and arranged in a percentile distribution to determine their observed 95th percentile values (Table II). The mean percent difference between area and volume determinations for each subject throughout the study was also computed (Table I). Each subject's mean percent area differences and mean area EF differences were regressed on the mean clinical grade of his 2-D images. Volume EF was regressed with the area EF from the same subject.

Ninety-five percent confidence limits for group data: The mean (± standard deviation) percent differences for end-diastolic area, end-systolic area, end-systolic volume, end-diastolic volume and mean differences for area and volume EF for the group were computed and tabulated (Table I). Ninety-five percent confidence limits for these group means were computed as: confidence limits = $t_{.05}$ (standard deviation)/$\sqrt{n}$, where t represents the t statistic for n-1 degrees of freedom at the 5% confidence level and n = the number of subjects.[1] (Table II).

Ninety-five percent confidence limits for individual subjects: The natural logarithms of end-diastolic and end-systolic area, end-diastolic and end-systolic volume, and area and volume EF values were entered into an analysis of variance to determine the within-subject's mean square differences (variance) over the 5 observations. This provided us with an estimate of the variability of serial recordings in a given subject. The 95% confidence limits for percent difference (variability) between observations of an echo measurement was calculated as $\log X_2 - \log X_1 = t_{(0.95,df)} \times \sqrt{2}$ (within-subject's variance), where X_1 and X_2 = 2 echo measurements in a given subject and df = degrees of freedom.[5,6] When the inverse log of both sides of the equation was taken, the computed 95% confidence limit equaled the ratio X_2/X_1, where X_2 is a measurement value that is greater than X_1. The $t_{(0.85,df)}$ = the 95th percentile value of the t statistic for the appropriate df. These data were converted to percent by taking the fractional portion of the X_2/X_1 ratio and multiplying by 100. Area and volume EF 95% confidence limits were converted from percent difference to difference by multiplying the confidence limit with the mean EF value computed by the analysis of variance (Table II).

Variability of repeated measurements of a cardiac cycle: One cycle from each subject was analyzed 3 times by the same observer using the Quantic 1200 to evaluate the variability (intraobserver) associated with the use of the computer image analysis system. The maximal percent differences noted between pairs of area and volume EF measurements were averaged. The 3 areas and area EF measurements for each subject were averaged and a coefficient of variation (standard deviation/mean) was calculated (expressed as percent). A mean coefficient of variation for the group was computed as the mean of all the subjects' individual coefficients of variation (Table III).

Results

The mean computer-generated midpapillary muscle short-axis end-diastolic area and end-systolic area were 16.39 ± 0.83 and 8.63 ± 0.47 cm^2, respectively. The mean area EF was 47.48 ± 5.13%. End-diastolic and end-systolic long-axis lengths were 8.4 ± 0.62 and 7.30 ± 0.61 mm, or a 14.04 ± 2.4% change during the cycle. The end-diastolic and end-systolic volumes calculated for these data were 116.93 ± 23.35 and 53.50 ± 12.11 ml, respectively. The volume EF was 54.50 ± 4.6%.

Regression of the area and volume EF revealed an excellent correlation (r = 0.98). However, regression of

TABLE II Observed and Predicted 95% Limits for Area, Volume and Ejection Fraction Differences

	End-Diastolic Percent Difference		End-Systolic Percent Difference		Ejection Fraction Difference (%)	
	Area	Volume	Area	Volume	Area	Volume
Observed 95th percentile values	17.3 (50)	17.4 (47)	15.2 (50)	17.8 (47)	11.0 (50)	9.5 (47)
95% confidence limit for a subject	16.8 (50)	16.7 (47)	15.8 (50)	17.0 (47)	12.8 (50)	9.7 (47)
Group 95% confidence limit	2.9 (10)	1.9 (10)	0.90 (10)	1.2 (10)	1.3 (10)	1.6 (10)

Numbers in parentheses indicate number of observations.

TABLE III Maximal Absolute and Percent Differences of Areas, Maximal Area Ejection Fraction Differences and Their Coefficients of Variation for Repeated Measurements of the Same Cycle

	End-Diastolic Area			End-Systolic Area			Area Ejection Fraction	
	Differences		CV	Differences		CV	Difference	CV
Sub.	cm^2	%	(%)		%	(%)	%	%
1	0.42	2.5	1.3	0.21	2.3	1.2	1.5	1.6
2	0.60	4.5	2.5	0.14	2.1	1.1	3.3	3.6
3	0.48	3.6	2.1	0.41	4.8	2.5	1.9	2.6
4	0.46	3.5	1.9	0.05	0.7	3.8	1.7	2.0
5	1.12	4.8	2.6	0.83	6.5	3.8	1.3	1.4
6	1.26	5.6	3.1	0.25	2.5	1.3	1.7	1.5
7	0.68	4.1	2.2	1.96	18.2	10.0	9.5	11.8
8	0.90	5.6	3.2	0.90	9.8	5.4	2.6	3.0
9	0.76	4.0	3.0	0.35	4.9	2.6	0.3	0.2
10	0.32	2.0	2.9	0.65	7.0	3.6	3.1	3.6
Mean	0.76	4.42	2.60	0.56	5.65	3.20	3.08	3.60
±SD	±0.38	±1.73	±0.90	±0.57	±3.80	±2.90	±2.40	±3.10

CV = coefficient of variation; SD = standard deviation; Sub. = subject.

mean clinical grade with end-diastolic area, end-systolic area and area EF revealed essentially no correlation, i.e., the r values were 0.14, 0.10 and 0.41, respectively.

Discussion

The variability of repeated measurements of LV volume and EF has been estimated using serial angiographic,[7,8] radionuclear ventriculographic and, more recently, echocardiographic[1–3,9,10] imaging in humans. Some studies[1–3] have shown greater variability of serial LV measurements in normal subjects than in patients with heart disease. Quantification of that variability in serial 2-D echocardiographic measurements not related to a disease process is necessary if 2-D echocardiography is to be used to follow changes in LV function. Serial LV volumes and EF were computed from an area-length equation using areas from manually traced endocardial borders of apical 4-chamber views on 2 days by Gordon et al[1] in 10 normal subjects and 20 patients with coronary artery disease. Their 95% confidence limits for percent change (computed as 2 times the standard deviation) were 15% between measurements of end-diastolic volume, 25% for end-systolic volume and 10% for EF to detect real changes, i.e., not owing to measurement error. However, confidence limits computed from their normal subject data was 16.3% for end-diastolic volume, 30% for end-systolic volume and 11.6% for EF. The present study was designed to simulate the variability one would expect from serial measurement of normal echocardiograms from different clinical laboratories. However, area measurements were made by a computer image analysis system to reduce variability due to observer bias in border identification.

Our study revealed that the predicted 95% confidence limits for percent differences encountered in the serial recording of echocardiograms for a given subject was 16.7% for end-diastolic volume, 17.0% for end-systolic volume and 9.70% for volume EF. While our individual and group 95% confidence limits for end-diastolic volume were similar to those found by Gordon et al,[1] those for end-systolic volume and volume EF were less than calculated for their normal subjects or their entire study group.

The differences between the confidence limits observed in both investigations may be related to a number of factors; the most significant is probably the method of border identification. The computer algorithm uses a thresholding technique to determine the peak gray levels indicating endocardial echocardiographic targets. On visual inspection, computer-generated borders appear to go through the midpoint of the leading edge of endocardial spots, a more important factor in end-systole when there is more coalescence and enlargement of the spots. Spot size or phosphor bloom around video images of echocardiographic targets have been related to gain amplification of the signal in the dynamic range of the echocardiograph.[11] Thus, this computerized method appears to choose consistent border points throughout the cycle that are relatively gain independent. In a previous study,[1] inner edge border points (the black-white endocardial interface) were used to reduce observer bias and increase consis-

tency of manually traced endocardial boundaries. This inner-edge technique has been noted to be gain-dependent in in vitro and in vivo studies.[12] Therefore, the larger variability of end-systolic volume noted by Gordon may be related to the gain dependence of their border identification method. However, the computer-generated areas are less open to subjective decisions made by the operator and therefore more consistent. This is shown in Table III, in which the maximal percent differences between values from repeated observation of the same cycle for the various area and area EF measurements ranged from 3.1 to 5.7%. The coefficients of variation for those repeated measurements ranged from 2.6 to 3.6%. The method for volume calculation in the prior study[1] required the imaging of an apical 4-chamber view. In this view the endocardial borders are less well seen in general (regardless of gain amplification) and this may have led to uncertainty of the location of the borders and contributed to the increased variability of volume calculations. Volume was calculated as $V = 8A(\frac{2}{3}\pi)L$, where A = long-axis area and L = long-axis length. In the present study, we used a short-axis view, which has more endocardial surface perpendicular to the interrogating echo beam and generally provides better definition of endocardial boundaries. Although 2 different area-length methods for determination of volume were used in each study, it is not clear that there is more variability associated with one or the other in terms of the volume calculations.

However, variability of area measurements will have a greater impact on volume and EF confidence limits, as area magnitudes (16.4 to 8.6 cm^2) and percent change (47.5%) during the cardiac cycle are greater than those for length (8.4 to 7.3 cm, 14%).

Our confidence limits of LV area and area EF are similar to those found for LV volumes and volume EF. The predicted 95% confidence of these measurements are very similar to the observed 95th percentile value measured from our study group. Also, there is an excellent correlation (r = 0.98) between area and volume EF. Similarly, the group area and volume-observed 95th percentile values and 95% confidence limits differed by 1% or less. In view of these findings, we propose that short-axis area and area EF could be used as indexes of LV function.

Our method has limitations: The use of LV short-axis cross sections, which may not be available in all patients, and the fact that our confidence limits were computed from an analysis of variance of measurements in a normal group. Although the limits are narrower than those previously observed,[1] other studies[1–3] have shown that the variability of serial measurements of LV volumes and EF can be greater in normal than in diseased hearts. Thus, the limits proposed by this study may not detect small differences between examinations because of disease in abnormal hearts. However, because of the significant variations in cardiac anatomy with different diseases that would affect area measurements differently and the different levels of ventricular dysfunction that can be found within a given category of cardiac disease, development of narrower confidence limits to detect smaller changes in abnormal hearts could be a complex and extremely difficult task. Therefore, the limits developed in this study may be the most clinically practical for computer-analyzed images.

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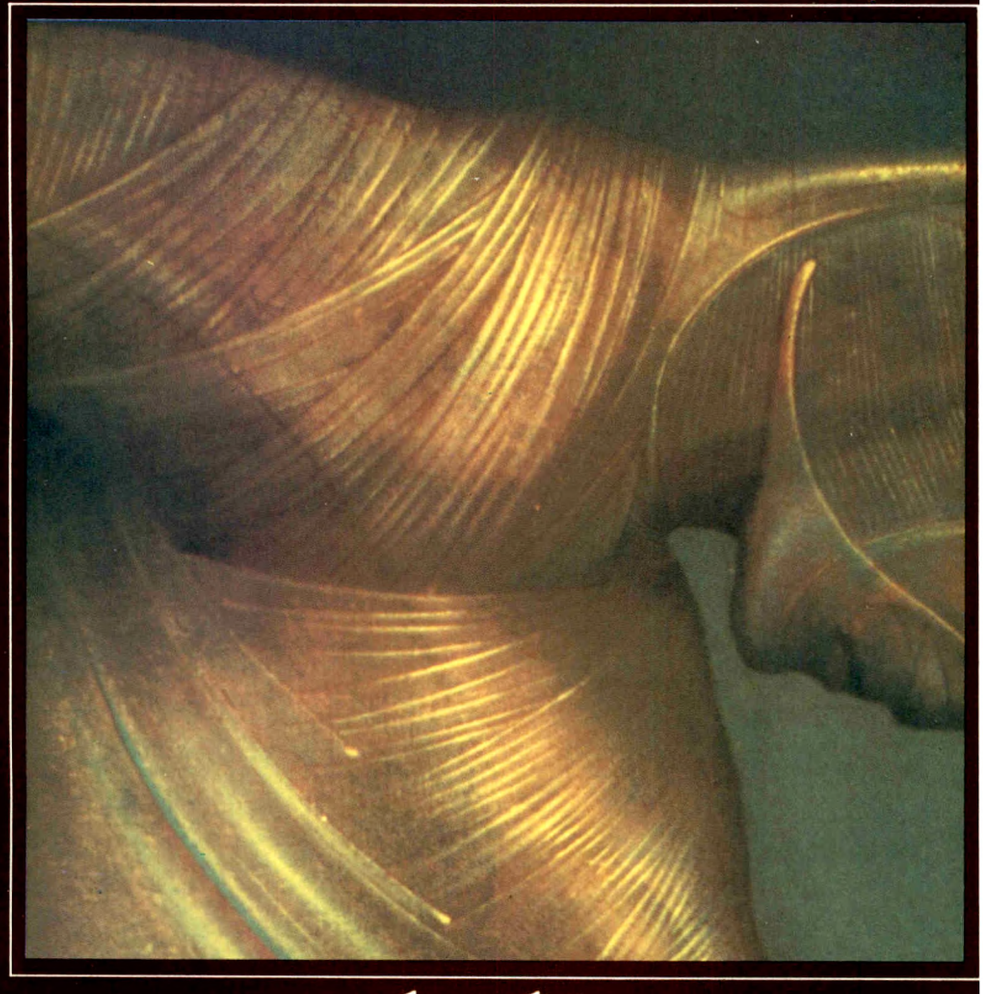
Between man and his medicine
lies only a thin barrier...



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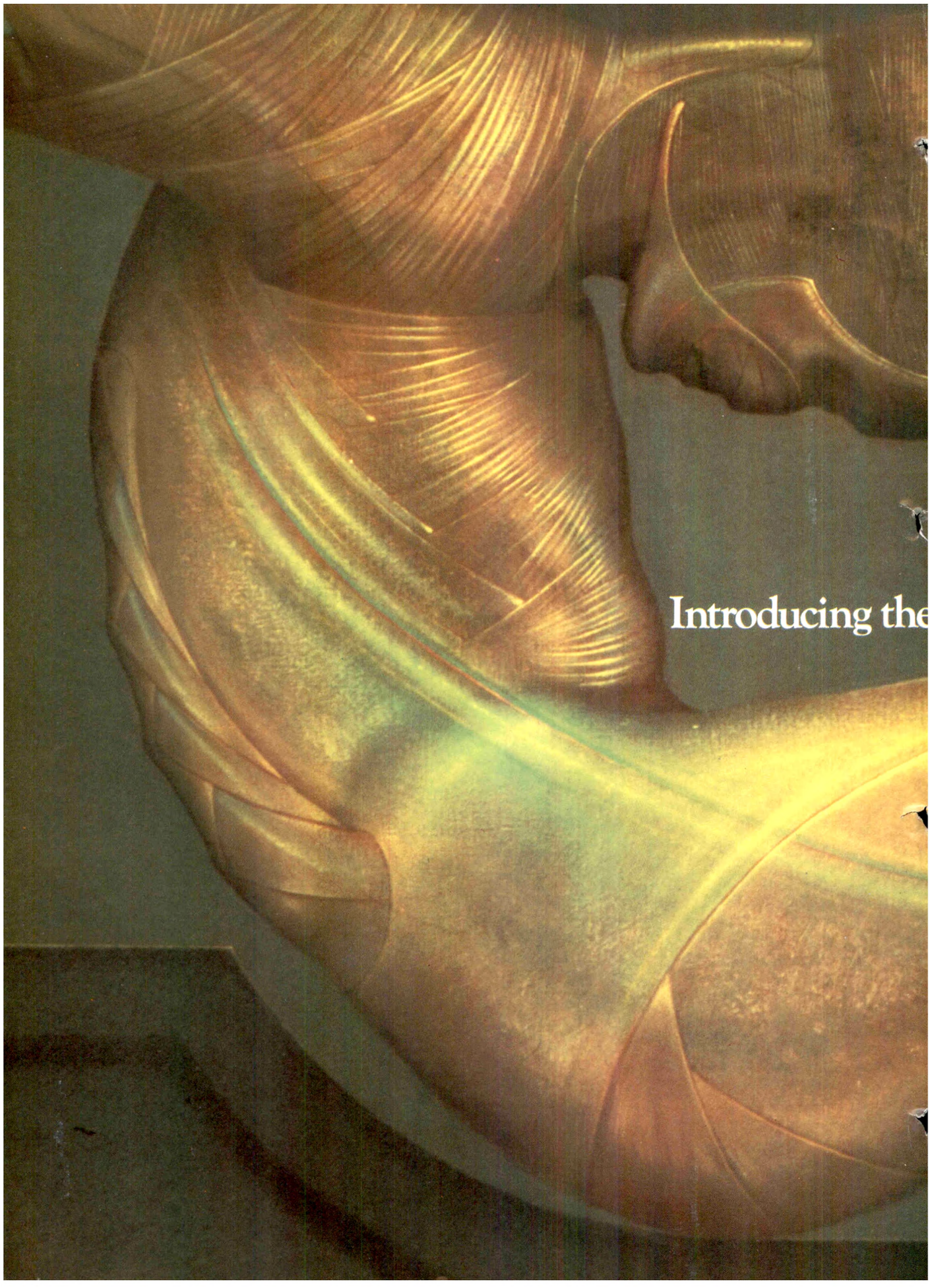
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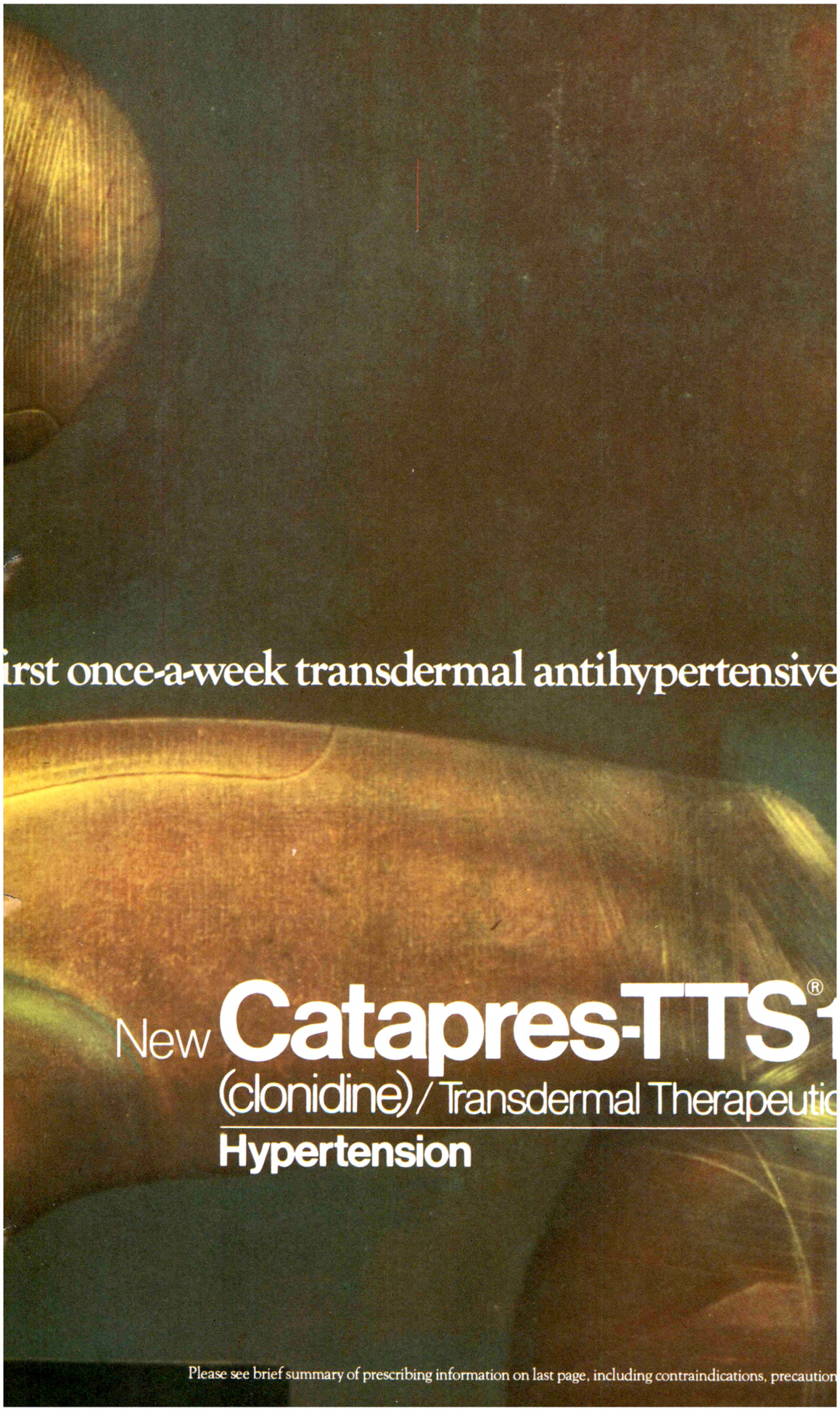
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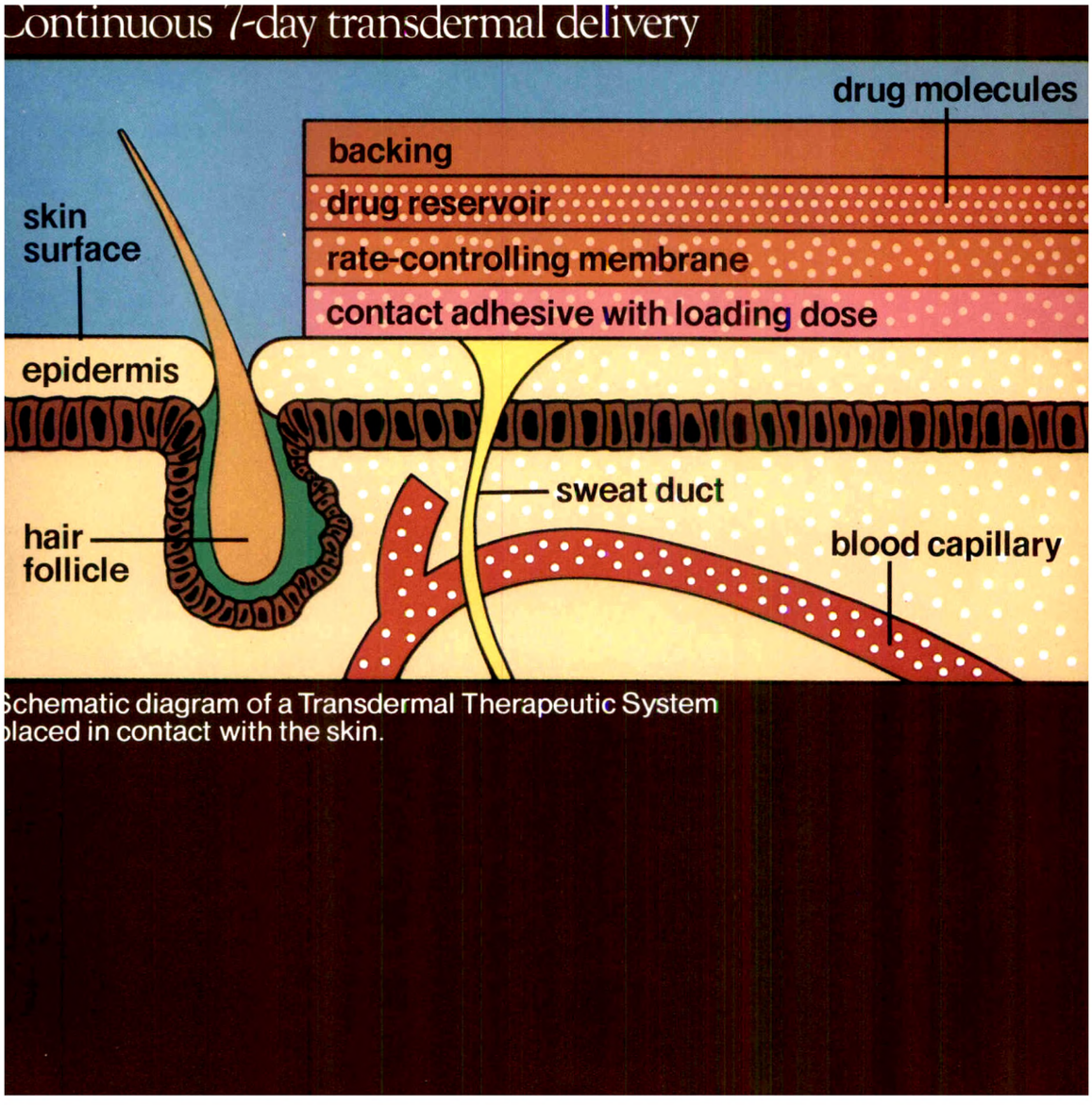
Please see brief summary of prescribing information on last page, including contraindications, precaution



Schematic diagram of a Transdermal Therapeutic System placed in contact with the skin.

New **Catapres-TTS**®[1,2,3]

(clonidine) / Transdermal Therapeutic System

Hypertension

Actual size patches

THREE DOSAGE STRENGTHS...
Start with it in mild to moderate hypertension

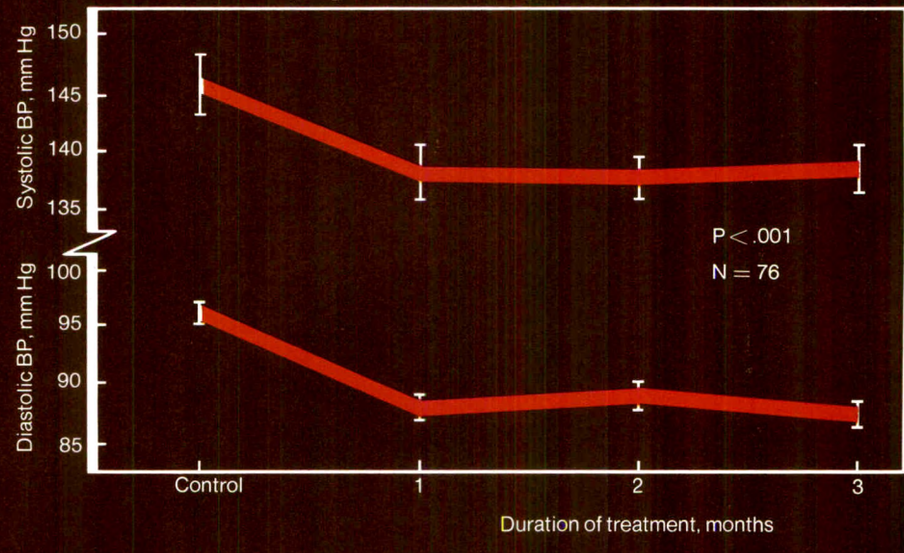
- Convenient once-a-week dosage to aid compliance.
- Effective blood pressure control with or without a diuretic.
- Steady-state blood levels — without the peaks and valleys of oral forms
- No diuretic-like biochemical effects.
- 24-hour blood pressure control 7 days a week.
- Central control of blood pressure.

Most common side effects are dry mouth and drowsiness, which tend to diminish with time, and mild erythema and pruritus associated with 7-day skin occlusion. After a mean duration of treatment of 24 weeks, contact dermatitis was observed in 16% of patients. This condition resolved upon discontinuation of therapy.

7 days of continuous therapy... a new age of compliance

Documented long-term efficacy

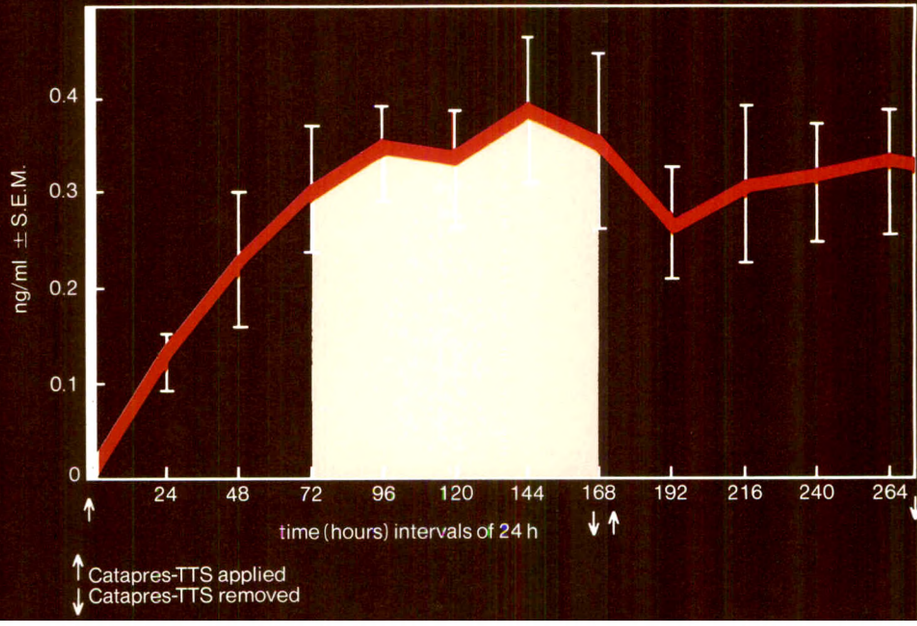
Systolic and diastolic BPs during control (placebo) and after 1, 2, and 3 months of treatment with clonidine administered transdermally. Values are means ± SEMs.[1]



Patch-to-patch applications

Steady-state blood levels— without the peaks and valleys of oral forms

Mean (n = 5) clonidine plasma concentration (ng/ml)—3.5 cm² Catapres-TTS patch.[2]



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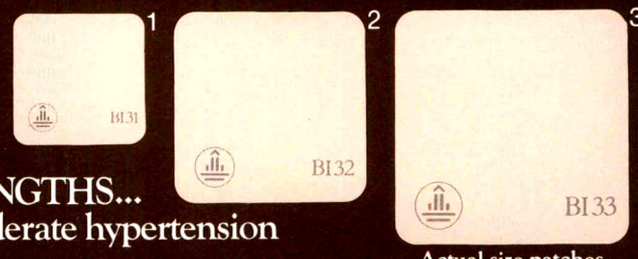
(clonidine) / Transdermal Therapeutic System

Hypertension



Actual size patches

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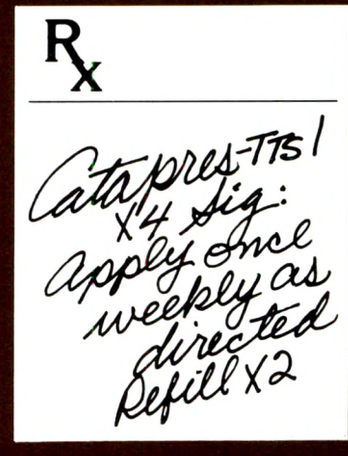
Titrate to proper dosage with Catapres-TTS® alone

1. Start with #1. Replace with #2 and then #3 when necessary to achieve effective blood pressure control.
2. Catapres-TTS® is usually unaffected by showering or other routine daily activities. For some patients, use of an overlay is occasionally required to maintain adequate skin adherence.
3. Most common side effects are dry mouth and drowsiness, which tend to diminish with time, and mild erythema and pruritus associated with 7-day skin occlusion. Contact dermatitis was observed in 16% of patients (100 of 631) treated for a mean duration of 24 weeks. This condition resolved upon discontinuation of therapy.*



*Please refer to **Precautions** in prescribing information if considering substitution of oral clonidine hydrochloride in patients who develop skin reactions during Catapres-TTS® therapy.

References:
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2. Data on file.

New

Catapres-TTS®1,2,3

(clonidine) / Transdermal Therapeutic System

Hypertension

Actual size patches

THREE DOSAGE STRENGTHS...
Start with it in mild to moderate hypertension

The first once-a-week transdermal antihypertensive system

seven days of effective blood pressure control

Convenient once-a-week dosage to aid compliance.
Effective blood pressure control with or without a diuretic.
Steady-state blood levels—without the peaks and valleys of oral forms

Brief Summary of Prescribing Information

Contraindications: Catapres-TTS® (clonidine) should not be used in patients with known hypersensitivity to clonidine or to any other component of the adhesive layer of the therapeutic system.

Precautions: ***General:*** In patients who have developed localized contact sensitization to Catapres-TTS® (clonidine), substitution of oral clonidine hydrochloride therapy may be associated with development of a generalized skin rash.

Patients who develop an allergic reaction to Catapres-TTS® that extends beyond the local patch site (such as generalized skin rash, urticaria, or angioedema) oral clonidine hydrochloride substitution may elicit a similar reaction.

As with all antihypertensive therapy, Catapres-TTS® should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

Withdrawal: Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in subjective symptoms such as nervousness, headache and sweating, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma, but such occurrences have usually been associated with previous administration of high oral doses (exceeding 1.2 mg/day) and/or with continuation of concomitant beta-blocker therapy. Rare instances of hypertensive encephalopathy and death have been reported.

An excessive rise in blood pressure following Catapres-TTS® discontinuance can be reversed by administration of oral clonidine or by intravenous phentolamine. If therapy is to be discontinued in patients receiving beta-blockers and clonidine concurrently, beta-blockers should be discontinued several days before cessation of Catapres-TTS® administration.

Perioperative Use: As with oral clonidine therapy, Catapres-TTS® therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting Catapres-TTS® therapy during the perioperative period should be aware that therapeutic plasma clonidine levels are not achieved until 2 to 3 days after initial application of Catapres-TTS®.

Information for Patients: Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a potential sedative effect of clonidine. Patients should be cautioned against interruption of Catapres-TTS® therapy without a physician's advice. Patients should be advised that if the system begins to loosen from the skin after application, the adhesive overlay should be applied directly over the system to assure good adhesion over its 7-day lifetime. Instructions for using the system are provided. Patients who develop moderate or severe erythema and/or localized vesicle formation at the site of application, or a generalized skin rash, should consult their physician promptly about the possible need to remove the patch.

Drug Interactions: If a patient receiving clonidine is also taking tricyclic antidepressants, the effect of clonidine may be reduced, thus necessitating an increase in dosage. Clonidine may enhance the CNS-depressive effects of alcohol, barbiturates or other sedatives. Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rabbits.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 132-week oral carcinogenicity study in rats, clonidine hydrochloride produced no carcinogenic effects at doses up to 300 times the maximum recommended human dose of Catapres-TTS® on a mg/kg weight basis.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Reproduction studies performed in rabbits at doses up to 3.1 times the maximum recommended daily human dose of Catapres-TTS® have revealed no evidence of impaired fertility or harm to the fetus due to clonidine hydrochloride. Studies in rats and mice revealed that doses of 500 mcg/kg/day and higher are embryotoxic. One rat study at doses of 15 mcg/kg/day (0.33 times the maximum recommended daily human dose) exhibited embryotoxicity. There are no adequate and well-controlled studies in pregnant women. Although animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: As clonidine is excreted in human milk, caution should be exercised when Catapres-TTS® (clonidine) is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

Adverse Reactions: Most systemic adverse effects during therapy with Catapres-TTS® (clonidine) have been mild and have tended to diminish with continued therapy. In a 3-month, multiclinic trial of Catapres-TTS® in 101 hypertensive patients, the most frequent systemic reactions were dry mouth (25 patients) and drowsiness (12 patients).

Transient localized skin reactions, primarily localized pruritus, occurred in 51 patients. Twenty-six patients experienced localized erythema. This erythema and pruritus were more common in patients utilizing an adhesive overlay for the entire 7-day treatment period. Allergic contact sensitization to Catapres-TTS® was observed in 5 patients.

In additional clinical experience, contact dermatitis was observed in 100 of 631 patients (about 16 in 100) treated for a mean duration of 24 weeks.

The following less frequent adverse experiences were also reported in patients involved in the multiclinic trial with Catapres-TTS®:

Gastrointestinal: Constipation (1 patient); nausea (1); and change in taste (1).

Central Nervous System: Fatigue (6 patients); headache (5); lethargy (3); sedation (3); insomnia (2); dizziness (2); and nervousness (1).

Genitourinary: Impotence/sexual dysfunction (2 patients).

Dermatological: Localized vesiculation (7 patients); hyperpigmentation (5); edema (3); excoriation (3); burning (3); papules (1); throbbing (1); blanching (1); and generalized macular rash (1).

In additional clinical experience involving 3539 patients, less common dermatologic reactions have occurred, where a causal relationship to Catapres-TTS® was not established: maculopapular skin rash (10 cases); urticaria (2 cases); angioedema involving the face (2 cases), one of which also involved the tongue.

Oro-otolaryngeal: Dry throat (2 patients).
In long experience with oral clonidine hydrochloride, the most common adverse reactions have been dry mouth (about 40%), drowsiness (about 35%) and sedation (about 8%). In addition, the following adverse reactions have been reported less frequently:

Gastrointestinal: Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; parotitis, rarely.

Metabolic: Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000; transient elevation of blood glucose or serum creatine phosphokinase, rarely.

Central Nervous System: Nervousness and agitation, about 3 in 100 patients; mental depression, about 1 in 100 and insomnia, about 5 in 1000. Vivid dreams or nightmares, other behavioral changes, restlessness, anxiety, visual and auditory hallucinations and delirium have been reported.

Cardiovascular: Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (i.e. conduction disturbances and arrhythmias) have been reported rarely.

Dermatological: Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.

Genitourinary: Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Other: Weakness, about 10 in 100 patients; fatigue, about 4 in 100; headache, and discontinuation syndrome, each about 1 in 100; muscle or joint pain, about 6 in 1000 and cramps of the lower limbs, about 3 in 1000. Dryness, burning of the eyes, dryness of the nasal mucosa, pallor, weakly positive Coombs' test, increased sensitivity to alcohol and fever have been reported.

How Supplied: Catapres-TTS®-1 (clonidine), Catapres-TTS®-2 (clonidine) or Catapres-TTS®-3 (clonidine) is supplied as 4 pouched systems and 4 adhesive overlays per carton.

Catapres-TTS®-1 or Catapres-TTS®-2 is supplied in a shipper of 3 cartons.

Consult package insert before prescribing.

CT-BPI-6/85

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Nd-YAG Laser Fusion of Human Atheromatous Plaque–Arterial Wall Separations in Vitro

JOHN F. HIEHLE, Jr., BS, DONNA B.C. BOURGELAIS, BS, STANLEY SHAPSHAY, MD, FREDERICK J. SCHOEN, MD, PhD, DUCKSOO KIM, MD, and RICHARD SPEARS, MD

The hypothesis that thermal fusion of disrupted layers of atheromatous arterial wall can be achieved with a neodymium-yttrium aluminum garnet (Nd-YAG) laser was tested. Fresh postmortem human atheromatous plaque was separated from the underlying arterial wall to simulate a dissection in 1-cm^2 arterial wall sections. With the plaque and underlying arterial wall subsequently compressed between glass slides, 17 W of continuous-wave Nd-YAG laser radiation were delivered through an optical fiber to the luminal surface of the plaque over a 4-mm^2 area. Fusion of the plaque to the underlying arterial wall invariably occurred when tissue compression was applied during lasing and a thin blood film was present between the tissues. The load supported by tissue welds depended on plaque thickness, plaque composition, and exposure duration and was as great as 25 g. In postmortem, blood-filled, whole-artery segments, in which plaque had been completely separated from the media, this technique was applied intraluminally during angioplasty with a prototype balloon catheter. Lateral dispersion of Nd-YAG radiation from the termination of an optical fiber within the balloon allowed fusion of plaque to the underlying arterial wall during balloon inflation to 2 atm. Histologic examination of laser-treated tissues showed coagulation of tissues at the junction between the intimal plaque and media. It is concluded that thermal fusion of separated layers of atheromatous arterial wall can be achieved with Nd-YAG laser irradiation. This concept may be useful in the treatment of arterial dissections.

(Am J Cardiol 1985;56:953–957)

Percutaneous transluminal coronary angioplasty (PTCA) is an effective technique for the treatment of obstructive coronary atherosclerosis in many patients.[1–3] However, widespread application of PTCA is limited by the occasional complication of abrupt reclosure,[4] which necessitates operative standby during the procedure. Furthermore, the frequent occurrence of restenosis of the treated arterial segment[5] greatly limits the long-term clinical benefits to be expected from this procedure.

An important mechanism underlying successful PTCA dilatation of an atheromatous narrowing involves disruption of tissues within the arterial wall, including plaque fracture,[6–8] and angiography immediately after PTCA frequently reveals either a shaggy or hazy appearance or evidence of dissection.[9] Although arterial wall disruption from PTCA is usually well tolerated acutely, it is likely that abrupt reclosure occasionally results from an adverse extension of this mechanism, such as enlargement of a false channel and collapse of plaque tissue into the lumen. Furthermore, restenosis may be accelerated by a disrupted luminal architecture, which may provide a thrombogenic surface and a nidus for new plaque growth. Therefore, techniques that reduce disruption of the arterial wall and improve luminal geometry after PTCA may improve the safety and efficacy of the procedure. Recently, the use of laser irradiation to effect tissue-to-tissue adhesion experimentally in vessel repair and anastomosis has had considerable success.[10,11] We therefore tested the hypothesis that neodymium-yttrium aluminum garnet (Nd-YAG) laser irradiation could be used to produce adhesion between separated layers of human atheromatous plaque and underlying arterial wall.

From the Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory of the Beth Israel Hospital, Department of Medicine, Cardiovascular Division, Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts; the Eleanor Naylor-Dana Laser Research Laboratory of the Lahey Clinic, Burlington, Massachusetts; and the Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Manuscript received December 26, 1984; revised manuscript received May 15, 1985, accepted May 17, 1985.

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Methods

Squares of arterial wall: An Nd-YAG laser (Advanced Biomedical Instruments), capable of 100 W of continuous-wave output at 1.06 μ was used for all studies. To evaluate the capability of Nd-YAG laser radiation to induce tissue to tissue adhesion, we exposed a series of separated layers of plaque and arterial wall to varying amounts of this radiation, and then quantitatively measured the strengths of the resultant adhesions.

In initial studies, we identified 2 factors that greatly facilitated laser fusion of tissue. One factor appeared to be application of firm pressure holding the layers of tissue in apposition during lasing. Sections of juxtaposed plaque and wall lased under no pressure exhibited no adhesion. The other

factor was the presence of a thin layer of blood between plaque and underlying arterial wall, which greatly improved the adhesion of these tissues. Therefore, all subsequent studies were performed with the application of pressure and with the presence of blood between the separated tissue layers.

Fresh postmortem human atheromatous aortas and iliac arteries were opened with a longitudinal incision and plaque was stripped from the underlying arterial wall. Plaque types were judged to be either fibrofatty or calcific by gross feel and appearance. The separated layers of plaque and outer arterial wall were then cut into squares of approximately 1 cm^2 each. Plaque thickness was measured with a micrometer caliper. We paired pieces of plaque and outer wall, being careful to preserve their original anatomic orientation, placed a small drop of fresh heparinized dog blood between the layers, and sandwiched the complex between 2 microscope slides held together with a spring clamp (Fig. 1).

Nd:YAG laser radiation was then directed perpendicularly toward the luminal surface of the sandwiched tissues via a 600-μ core optical fiber, the end of which was maintained at a fixed distance 1 cm from the surface of the glass slide during laser exposure. The He-Ne reference beam illuminated a spot size of approximately 2 mm in diameter, and the power output from the optical fiber was adjusted to 17 W. This peak power resulted in a nominal power density of about 500 to 600 W/cm^2 without considering reflection of unknown magnitude from the glass microscope slide and the luminal plaque surface. However, because of scattered radiation and thermal diffusion, the functional size of the tissue region heated by the laser radiation was considerably greater than the nominal 2-mm spot size of the reference beam. Indeed, the temperature of tissue at a distance of 2 mm from the edge of the reference spot plateaued at 58°C, as measured with a thermistor mounted on a 25-gauge needle (Yellow Springs Instrument Corp.) after 10 seconds of lasing. After irradiation, welded sets of tissue were stored in saline solution at 4°C before strength testing or histologic evaluation.

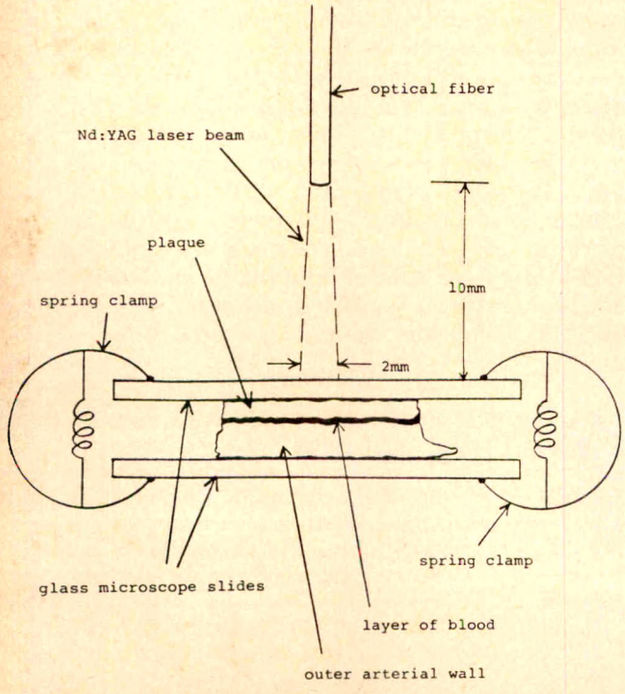

FIGURE 1. Experimental setup for laser fusion of sections of plaque and underlying arterial wall.

To quantitate the strength of the laser-induced welds, the tissues were subjected to gradually increasing loads until the welds separated. The loading was performed by cementing the adventitial surface of the artery to a stiff support with cyanoacrylate adhesive (Crazy Glue™) and suspending weights from a 4-0 silk suture sewn through the flaps of plaque on either side of the weld. The maximal weight that could be suspended from the suture was used as a measure of the strength of the weld.

Specimens for histologic evaluation were fixed in 10% formalin, embedded in plastic, and sections were stained with hematoxylin-eosin.

Segments of whole artery: The efficacy of applying intraluminal Nd-YAG laser radiation from an inflated balloon to weld separated layers of plaque and underlying arterial wall was tested in fresh, whole, postmortem human atheromatous iliac arteries cut transversely into 2-cm-long segments. For each of the 6 segments studied, the inner layer of plaque was dissected completely from the outer layer of arterial wall without cutting through either the plaque or the outer wall before laser treatment (Fig. 2, a and b).

A prototype balloon catheter was constructed from silicone-based materials that were relatively transparent to Nd-YAG laser radiation and that were unaffected by high temperatures (more than 100°C). The 600-μ core of the optical

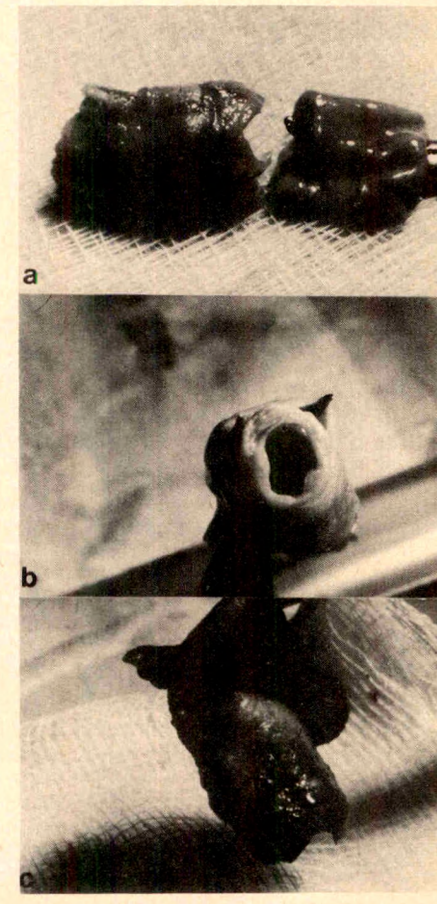

FIGURE 2. a, segment of artery in which a concentric plaque has been separated from the outer arterial wall. **b,** same segment as in **a,** with the plaque and outer arterial wall in apposition. **c,** after laser treatment and longitudinal incision. The arterial segment is held by a hemostat clamped to the outer arterial wall and the plaque is supported solely by a laser-induced tissue weld.

TABLE I Results of Attempts to Weld Squares of Arterial Wall (Including Only Those Plaques Lased with the Application of Both Pressure and Blood Between the Layers)

Specimen	Plaque Thickness (mm)	Plaque Calcification	Exposure Duration (sec)	Maximal Weld Load (g)*	Vaporization
1	0.5	0	5	0†	0
2	0.5	0	10	19.1	0
3‡	0.5	0	10	7.1	0
4	0.5	0	15	12.6	0
5‡	0.5	0	15	11.1	0
6	0.5	0	20	. . .§	0
7‡	0.5	0	20	15.1	+
8	0.5	0	25	20.6	0
9	0.5	0	25	2.3	+
10	1.4	+	10	0†	+
11	1.5	+	15	19.1	+
12	2.1	+	20	. . .§	0
13	2.3	+	25	25.6	0
14	1.5	+	32	0†	+
15	2.3	+	Multiple¶	0†	0
16	1.7	+	Multiple¶	0†	+

* [Maximal supported load + load at weld separation]/2.
† Adhesion too weak to quantitate.
‡ Extra layer of blood applied to the intimal surface.
§ Used for histologic examination.
¶ Multiple laser exposures applied.
0 = absent; + = present.

fiber used to transmit the 1.06-μ radiation terminated within the balloon in a 5-mm-long diffusing tip that provided radially directed dispersion of the radiation around the circumference of the balloon.

Before inserting the balloon catheter into an arterial segment, fresh heparinized human blood was injected into the lumen and between the separated layers of plaque and arterial wall. The deflated balloon was then inserted into the lumen and fluid-inflated to approximately 2 atm of pressure. The diameter of the inflated balloon was 8 mm, slightly larger than the luminal diameter of the arterial segments. Laser exposure at 20 W was then performed for 18 to 40 seconds, beyond which duration the onset of tissue vaporization occurred. After laser exposure, the artery was permitted to cool for 5 to 10 seconds before deflating the balloon and removing the balloon from the arterial segment.

The segments were then sliced longitudinally and submitted to testing for weld strength in a manner identical to that described earlier.

Results

Squares of arterial wall: The strength of tissue welds for a given exposure duration depended, in part, on plaque thickness and composition (Table I). Thick, calcific plaques generally formed weaker adhesions than thin, fibrofatty plaques, but because most of the thick plaques were also calcific, we could not separate the importance of these 2 variables. Exposure duration was another important variable; weld strength was roughly proportional to lasing duration, with some welds supporting as much as 20 to 25 g (Fig. 3). Vaporization usually resulted from a lack of pressure on the tissue or from a long lasing duration, but also occurred when a plaque was hemorrhagic in appearance. The onset of vaporization was accompanied by a characteristic high-frequency sound. A thin layer of blood on the intimal surface had little or no effect on weld strength.

Histologic examination of the vessel wall segments revealed multifocal zones of adherence within the media of the treated vessel (Fig. 4). There was a generalized mild tissue coagulation throughout the vessel wall, which was most prominent in the junctional zone. Furthermore, there was prominent fat necrosis at the adventitial surface.

Segments of whole artery: Of the 6 segments tested, 3 exhibited no adhesion, 1 slight adhesion (supporting 8 g) and 2 excellent adhesion (supporting 70 g and 165 g). Two of the 3 that exhibited no adhesion were lased for less than 20 seconds. During irradiation of a segment, the arterial wall appeared to shrink at the smaller ends of the balloon and mold itself to the shape of the balloon. After exposure, the wall seemed stiff and inelastic, having a rubbery consistency. The welds formed in these whole artery segments were nonuniform about the circumference of the artery, most likely as a result of nonuniformity of radiation scatter within the prototype

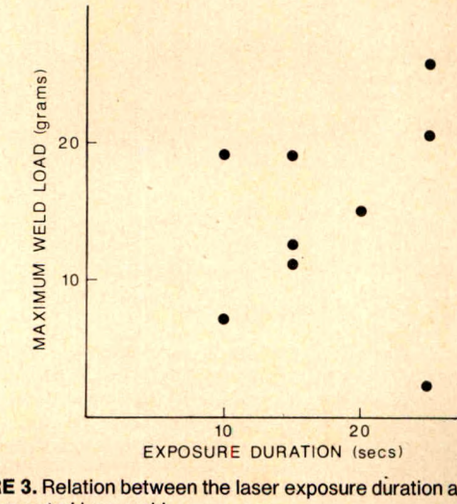

FIGURE 3. Relation between the laser exposure duration and the total load supported by a weld.

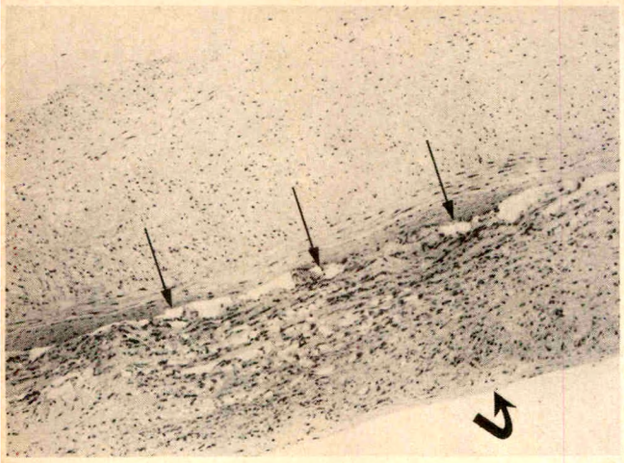

FIGURE 4. Histologic section of welded iliac artery showing zone of adhesion. The entire cross section of the artery is shown; the luminal surface is indicated by the **curved arrow** and line of weld zone is indicated by **straight arrows.** The junctional zone is within the longitudinal medial smooth muscle layer. Hematoxylin-eosin stain; magnification ×80, reduced 66%.

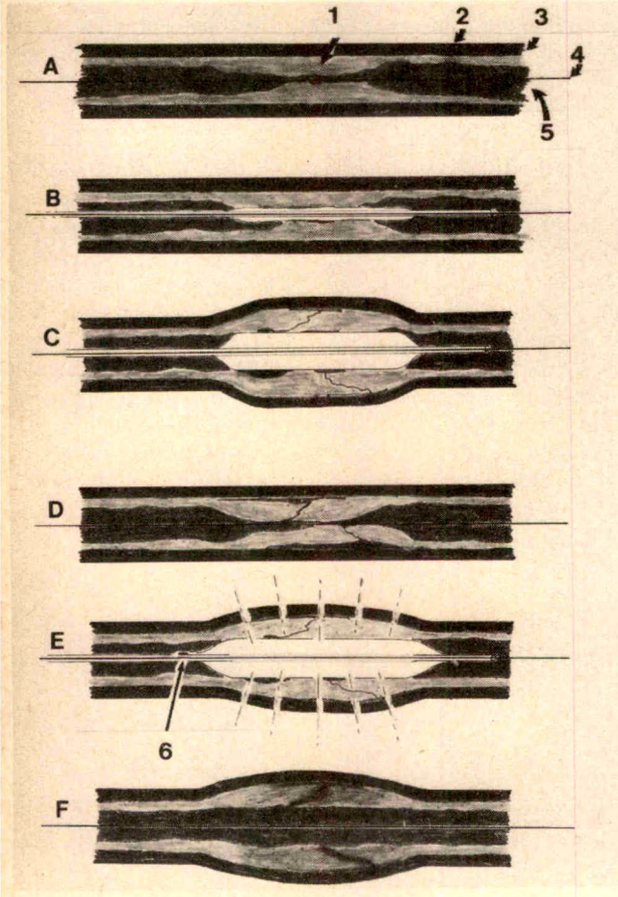

FIGURE 5. A to **C,** conventional balloon angioplasty in which a guidewire (4) is inserted into the arterial lumen (5). The balloon is threaded over the guidewire to the obstructing plaque (1) and inflated, sometimes causing dissection of the arterial wall to the media (3) or occasionally even the adventitia (2). Extensive dissection may cause abrupt reclosure (**D**). In this instance, laser balloon angioplasty (**E**) may be useful in fusing dissected layers of arterial wall, resulting in a smooth, dilated lumen (**F**). Lasing complications may be avoided by using an acoustic sensor (6) to detect the onset of tissue vaporization.

balloon. The balloon itself was unaffected by the laser radiation and there was neither adhesion between the balloon and the intimal surface nor thrombus formation at either end of the balloon.

Discussion

Although the mechanism of laser-induced tissue fusion is not clearly understood, investigators have postulated that a heat-induced shrinkage and cross-linking of tissue proteins may partially explain the phenomenon.[11] Others have shown that the arterial wall would shrink when heated, and that, in fact, the elastic resistance of the tissue actually increases with temperature.[12,13] Unrestrained, this shrinkage would lead to a reduction in the size of the luminal cross-sectional area. However, with an inflated balloon maintaining luminal size in the present study, the shrinkage had the effect of compressing the inner wall and improving adhesion of disrupted elements. By maintaining balloon inflation for 5 to 10 seconds after cessation of laser irradiation, no further tissue shrinkage occurred on balloon deflation. Furthermore, the artery showed no recoil on balloon deflation, and the luminal diameter equal to that during maximal balloon inflation was maintained.

Despite the coagulative properties of Nd-YAG laser radiation, thrombus formation within the lumen of the whole arteries was not a problem because the inflated balloon displaced blood from the luminal surface. The proximal and distal ends of the balloon, which were in direct contact with blood, were not exposed to the laser radiation, so that coagulation of blood at these locations could be avoided.

Fusion of thick, calcified plaque to the underlying wall may require a laser exposure duration that may not be markedly shorter at the power densities used herein than the exposure duration resulting in the onset of tissue vaporization. The latter, if continued, could cause vessel perforation or result in aneurysm formation.[14,15] Significant vaporization might be avoidable by terminating lasing on detection of the high frequency sound generated at the onset of vaporization (Fig. 5).

Refinements in balloon catheter and optical fiber materials and designs is needed to construct an optimal laser delivery system during balloon angioplasty. In addition, although tissue healing after laser-induced vascular anastomosis[10] and intraluminal laser-induced injury to the arterial wall[16] is excellent in experimental studies, the acute and chronic in vivo effects of Nd-YAG irradiation on the normal and atherosclerotic wall as performed in the present study must be characterized. However, these preliminary results suggest that the proposed catheterization technique is effective and implementable. If in vivo studies are similarly encouraging, laser balloon angioplasty may be useful for treating both spontaneously occurring and PTCA-induced arterial dissections. This application, coupled with the potential for an improved vessel dilatation, should result in an improved luminal geometry and may reduce the incidence of both abrupt reclosure and restenosis associated with PTCA.

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Circulatory Effects of Coffee in Relation to the Pharmacokinetics of Caffeine

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Drinking coffee results in an increase in blood pressure (BP) after an interval of caffeine abstinence. During chronic caffeine intake this pressor response disappears and adaptation to the circulatory effects of caffeine develops. This study was designed to determine whether a pressor response to coffee occurs during chronic caffeine intake if low basal plasma caffeine levels are achieved by a period of caffeine abstinence, defined by individual plasma caffeine half-life. In 8 normotensive subjects, circulatory measurements were studied after ingestion of coffee in 2 strengths, decaffeinated coffee and hot water after a caffeine abstinence of 4.5 times individual caffeine half-life. These measurements were compared to the same protocol without intervention. Coffee of both strengths resulted in a similar increase in BP (diastolic BP ± 15%). The coffee-induced increase in forearm blood flow and plasma epinephrine levels were less pronounced. Decaffeinated coffee induced a smaller increase of diastolic BP, and after water, no changes were observed. Additionally, a negative correlation was found between the coffee-induced BP increase and basal plasma caffeine level in a group of 30 normotensive subjects ($r = -0.71$, $p < 0.001$). During chronic caffeine intake, subjects with short plasma caffeine half-life are exposed to a pressor response after drinking coffee, despite the phenomenon of adaptation.

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Because caffeine and coffee are widely consumed throughout the world, a relation between coffee and blood pressure (BP) would be of clinical interest.[1,2] Recent studies have reported a positive association between BP and coffee consumption.[3,4] There is also pharmacologic evidence for a BP-increasing effect of caffeine and coffee.[5–7] The relevance of these observations to the effect of daily coffee use on BP was questioned by some investigators.[8,9] According to these studies complete adaptation or tolerance to the circulatory effects of caffeine develops during chronic caffeine use. However, in 1 study there was evidence that cardiovascular reactivity to caffeine was greater in subjects with initial caffeine levels of less than 1 mg/liter than for those with basal plasma caffeine levels of more than 1 mg/liter.[8] This means that the development of tolerance to the effects of coffee depends on prior caffeine use and on the individual pharmacokinetics of caffeine. In healthy subjects, elimination half-life ($T_{1/2}$) of plasma caffeine varies between 1.5 and 9.5 hours.[10] To determine whether coffee increases BP during chronic caffeine ingestion, the time of caffeine abstinence before the test must be related to individual pharmacokinetics of caffeine. We studied the circulatory effects of drinking coffee after a period of caffeine abstinence related to individual plasma caffeine $T_{1/2}$ in 8 normotensive subjects. Hemodynamic and humoral effects of 2 strengths of coffee, and of equal amounts of decaffeinated coffee and water of the same temperature were compared to a similar protocol without intervention. In 30 other normotensive subjects, we analyzed the relation between basal plasma caffeine level and the coffee-induced increase in BP.

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Methods

Eight normotensive, healthy subjects (5 men, 3 women) gave informed consent for this study, which was approved by the hospital ethical committee. The mean age was 23.4 years (range 21 to 25), height 180.4 cm (range 169 to 201) and Quetelet index 21.5 kg/m^2 (range 17.9 to 24). All subjects were accustomed to daily coffee ingestion, and mean estimated coffee use ranged from 4 to 9 cups/day. Three men were habitual smokers and all women used oral contraceptive drugs.

The first part of the study was a pharmacokinetic analysis of all subjects. Before and after drinking 2 cups of coffee, blood

samples were drawn for determination of plasma caffeine concentration. After coffee ingestion, blood was sampled every 20 minutes for 2 hours, and afterward another 3 times distributed over about 20 hours. From these data, time of plasma peak level (Tm) was registered and the elimination caffeine $T^1/_2$ was calculated. As $T^1/_2$ and Tm do not differ within an individual after different doses of oral caffeine, a single measurement of these values was sufficient.[10]

After this pilot study every subject took part in 5 tests, which were ordered at random and separated from each other by at least 1 week. All tests had the same protocol, different only in the kind of intervention: similar amounts of regular coffee, stronger coffee, decaffeinated coffee, hot water and "no intervention." For the tests with regular, strong and decaffeinated coffee the protocol was single-blind, but as a matter of course this could not be realized for the tests with hot water and no intervention. Before all tests were performed, the subjects had to abstain from all caffeine-containing products for a period of 4.5 half-lives. At the beginning of this period 200 mg of caffeine were ingested (as tablets) to be sure that abstinence was not longer than 4.5 half-lives. The subjects were not allowed to smoke for 8 hours before the tests and a light caffeine-free breakfast was allowed between 7:30 and 8:00 AM.

All tests were performed from 8:15 to 11:15 AM with the subject in the supine position. The first 30 minutes served as an equilibration period to reach basal hemodynamic and humoral values. In this period an Arteriosonde 1225 (semiautomatic BP monitor) and a mercury strain-gauge venous occlusion plethysmograph (forearm blood flow registration) were connected to the subject's left arm. Because we only wanted to measure muscle flow, a wrist cuff was inflated during the measurements to block the skin flow of the hand. Heart rate was measured by electrocardiogram. An antecubital vein of the right arm was cannulated and blood samples were taken for determination of plasma caffeine, renin and norepinephrine concentrations just before intervention, at the individual Tm and 120 minutes after intervention. After the first 30 minutes of equilibration, systolic and diastolic BP and heart rate were measured every 5 minutes for 30 minutes. In between these measurements, 4 series of 3 forearm blood flow recordings were made and blood was sampled. Subsequently the subjects had to drink 300 ml of a beverage within 10 minutes in the supine position with the aid of a straw (except in the no-intervention test). All beverages were prepared using a coffee machine with 300 ml of water and, depending on the test, 25 g of coffee (strong coffee), 17.5 g of coffee (regular coffee), 17.5 g of decaffeinated coffee and no coffee (hot water test). Then, systolic and diastolic BPs and heart rate were recorded every 5 minutes for 2 hours, and again a series of 3 forearm blood flow registrations were made in between.The protocol of the tests is illustrated in Figure 1.

In 30 other normotensive and healthy subjects we also studied the hemodynamic effects of coffee. The same protocol as in the regular coffee test was used. For these subjects, however, the time of caffeine abstinence was arbitrary and not related to plasma caffeine $T^1/_2$. We used this group to study the relation between basal plasma caffeine levels and pressor responses to coffee. In these subjects we did not sample blood for determination of plasma catecholamines or plasma renin activity.

Plasma concentrations of caffeine were analyzed with a reversed-phase high-performance liquid chromatography method.[6] Plasma catecholamine levels were measured by a radioenzymatic assay,[11] and plasma renin activity by radioimmunoassay.[12]

Statistical analysis: Hemodynamic variables before intervention were averaged for each subject to 1 basic value, and after intervention to 1 value for every period of 20 minutes. Differences between the 20-minute-period values and the basic value were averaged for each subject, resulting in 1 mean change over the 2-hour period. In the statistical analysis these mean changes induced by strong, regular or decaffeinated coffee or hot water were compared with the results of the no-intervention test by Student *t* test for paired observations (2-sided). Humoral variables were analyzed by comparing values after intervention with basal values by the paired Wilcoxon test (2-sided). The fractional changes in the 5 tests also were compared with each other. Correlation coefficients were calculated according to Pearson. Mean arterial pressure was calculated as the sum of diastolic BP and one-third of pulse pressure, and forearm vascular resistance was calculated by dividing mean arterial pressure through forearm blood flow. Forearm vascular resistance is expressed in arbitrary units. All results are presented as mean ± standard error of the mean.

Results

The results of the preliminary pharmacokinetic measurements are shown in Figure 2. Peak plasma caffeine concentrations were reached in 4 subjects in the first, in 1 in the third, in 2 in the fourth and in 1 in the fifth 20-minute period after coffee. The mean Tm was 50 ± 12 minutes. Calculated $T^1/_2$ ranged from 2 to 8.5 hours (mean 4.2 ± 0.8). The caffeine abstinence period for the 5 tests ranged from 9 to $38^1/_4$ hours. In the pilot study the mean peak plasma caffeine level was 4.3 ± 0.6 mg/liter. Figure 2 shows that plasma caffeine levels are almost in a steady state during the tests.

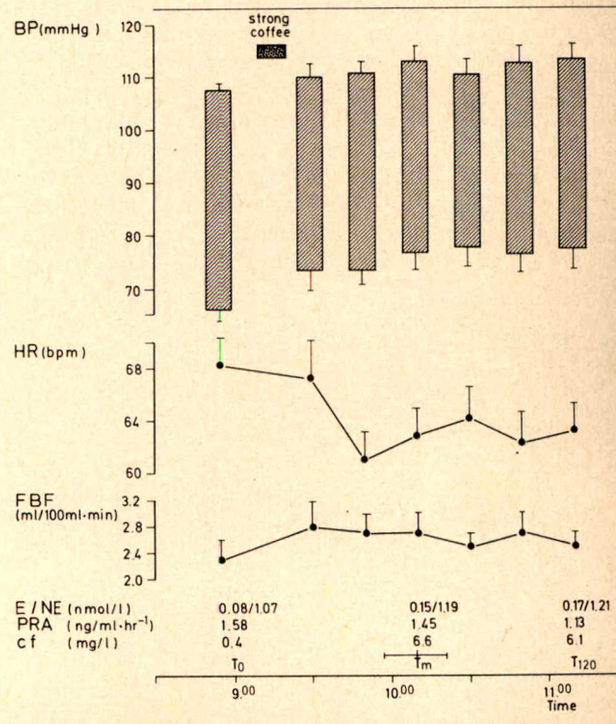

FIGURE 1. Schedule of measurements in 8 subjects after drinking strong coffee. Mean values (± standard error of the mean) of blood pressure (BP), heart rate (HR) and forearm blood flow (FBF) before and for 6 periods of 20 minutes after coffee ingestion are given. Plasma concentrations of norepinephrine, epinephrine (NE, E), renin (PRA) and caffeine (cf) were measured 3 times. Tm = time of plasma peak level.

TABLE I Basal Values of all Hemodynamic Parameters in the Five Tests

	NI	W	DC	RC	SC
Systolic blood pressure (mm Hg)	110 ± 2	111 ± 2	113 ± 2	110 ± 2	108 ± 1
Diastolic blood pressure (mm Hg)	72 ± 2	68 ± 3	67 ± 2	66 ± 3	66 ± 2
Mean arterial pressure (mm Hg)	85 ± 2	83 ± 2	82 ± 2	81 ± 2	81 ± 2
Heart rate (beats/min)	72 ± 3	73 ± 3	72 ± 3	73 ± 3	68 ± 2
Forearm blood flow (ml/100 ml·min)	2.5 ± 0.2	2.7 ± 0.3	2.7 ± 0.3	2.6 ± 0.3	2.3 ± 0.3
Forearm vascular resistance (U)	37 ± 4	34 ± 5	34 ± 4	36 ± 6	40 ± 6

All values are mean ± standard error of the mean.
DC = decaffeinated coffee; NI = no intervention; RC = regular coffee; SC = strong coffee; W = water.

In Table I all basal hemodynamic data of the 5 tests are listed, and these values revealed no statistically significant differences. Mean changes over the 2-hour period of systolic and diastolic BPs, heart rate and forearm blood flow in the 5 experimental situations are shown in Figure 3. In the regular and strong coffee tests, the systolic BP increase measured 4 ± 1 and 5 ± 2 mm Hg, respectively; these increases were significantly higher than those in the other tests. The same applied to the increases in diastolic BP of 8 ± 1 and 9 ± 1 mm Hg, respectively, and in mean arterial pressure of 7 ± 1 mm Hg in both tests. Figure 4 shows that the increase in BP was maximal in the last hour. In the regular and strong coffee tests, the percent increase in diastolic BP in the last 20-minute period was 16 ± 3% and 15 ± 4%, respectively. After ingestion of regular coffee, the individual maximal increase in mean arterial pressure ranged from 8 to 19% and after strong coffee from 8 to 15%. There was no relation between the individual increase in mean arterial pressure and the corresponding time of caffeine abstinence. After ingestion of decaffeinated coffee, a smaller increase in diastolic BP was observed, whereas drinking water did not induce any changes. In all tests a decrease in heart rate was observed, and after water, regular coffee and strong coffee, these decreases were greater than those after the no-intervention test ($p < 0.10$); they were 5 ± 1, 7 ± 2 and 5 ± 1 beats/min, respectively. Without intervention, mean heart rate decreased by 2 ± 1 beats/min (Fig. 3). There was a significant difference between the increase in forearm blood flow of 0.3 ± 0.2 ml/100 ml·min after strong coffee intake and the decrease of 0.2 ± 0.2 ml/100 ml·min during the water and decaffeinated coffee test. As a consequence mean forearm vascular resistance decreased 2.1 ± 2.8 U during the strong coffee test, which was different from the increase in forearm vascular resistance of 3.6 ± 2.1 and 3.5 ± 2.1 U after hot water and decaffeinated coffee ($p = 0.03$, $p = 0.07$).

Figure 5 shows all humoral measurements of the 5 tests. Individual basal plasma caffeine levels of these tests were all within the range of less than 0.1 to 2.0 mg/liter, independent of the time of caffeine abstinence ($n = 40$, $r = -0.25$, $p > 0.1$). After ingestion of strong and regular coffee, a significant increase in plasma caffeine levels to 6.6 ± 0.4 and 5.2 ± 0.9 mg/liter was observed, the former being significantly greater than the latter ($p < 0.005$). In the hot-water and no-intervention tests, plasma caffeine concentration showed a small but significant decrease of 0.2 mg/liter at the end of the tests;

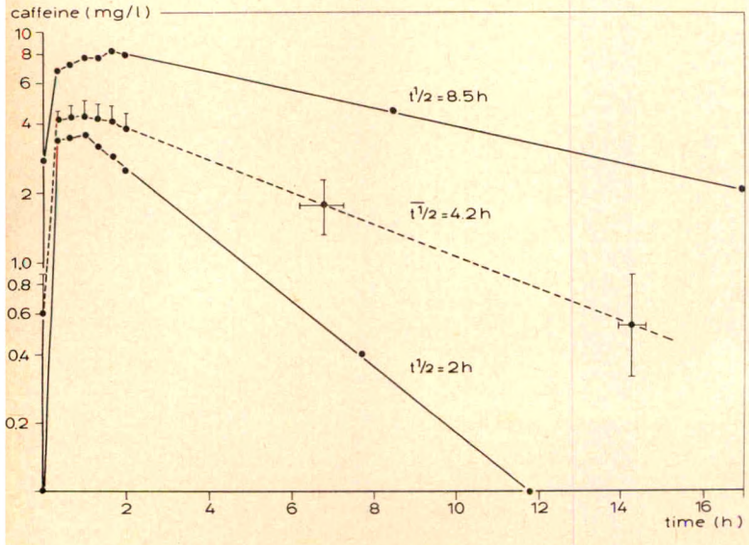

FIGURE 2. Course of plasma caffeine levels in subjects after drinking coffee. Mean results (± standard error of the mean) as well as the results of the subjects with the shortest and longest elimination half-life ($t_{1/2}$) of caffeine are given.

after decaffeinated coffee was ingested, no significant change was observed. Table II lists the mean fractional changes of plasma catecholamine levels. Changes in plasma norepinephrine levels were about the same among the 5 tests. Plasma epinephrine levels, however, increased more significantly after consumption of regular and strong coffee than after decaffeinated coffee. Plasma epinephrine levels and plasma renin activity were significantly different during all tests compared with basal values. The percent reduction of plasma renin activity after drinking decaffeinated coffee ($-17 \pm 7\%$), regular coffee ($-19 \pm 7\%$) and strong coffee ($-18 \pm 5\%$) was smaller than after drinking hot water ($-33 \pm 5\%$, $p < 0.10$). In the 4 tests in which a beverage was ingested, there was a significant correlation between the increase in plasma caffeine and the fractional increase in mean arterial pressure ($n = 32$, $r = 0.70$, $p < 0.001$). The fractional increase in plasma epinephrine weakly correlated with changes of plasma caffeine ($n = 32$, $r = 0.36$, $p < 0.05$).

Figure 6 shows the most relevant results of the second part of the study. In the 30 subjects, a strong correlation was observed between basal caffeine level and the increase in mean arterial pressure in the second hour after drinking coffee (^{10}log (caffeine) vs mean arterial pressure: $n = 30$, $r = -0.71$, $p < 0.001$). Mean increase in mean arterial pressure measured $7 \pm 1\%$ (range -1 to 24%). Because of the arbitrary time of caffeine abstinence, there was also a large range of basal plasma caffeine levels (less than 0.1 to 6.3 mg/liter, mean 1.0 ± 0.3).

Discussion

Under experimental conditions there is clear evidence for a BP-increasing effect of caffeine,[5–7,13,14] but during chronic ingestion of caffeine no cardiovascular response to caffeine or coffee occurred.[8,9] In 1968, Colton et al[15] suggested that this tolerance could partly ex-

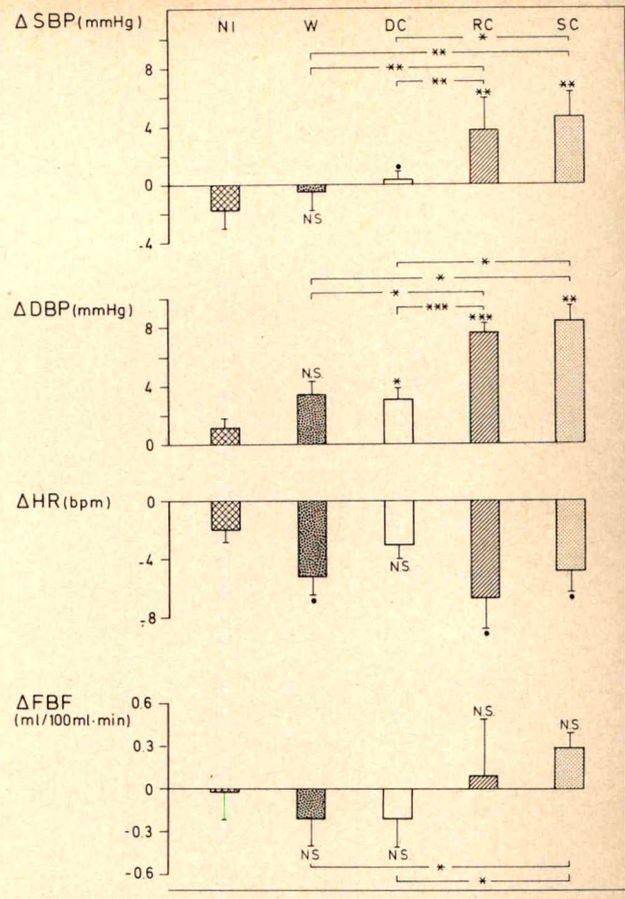

FIGURE 3. Mean changes over the 2-hour period of systolic and diastolic blood pressure (SBP, DBP), heart rate (HR) and forearm blood flow (FBF) after no intervention (NI), consumption of water (W), decaffeinated coffee (DC), regular coffee (RC) and strong coffee (SC) (mean ± standard error of the mean). **Asterisks** represent significances with respect to no intervention, unless signed otherwise. bpm = beats/min; NS = not significant; • $p < 0.10$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

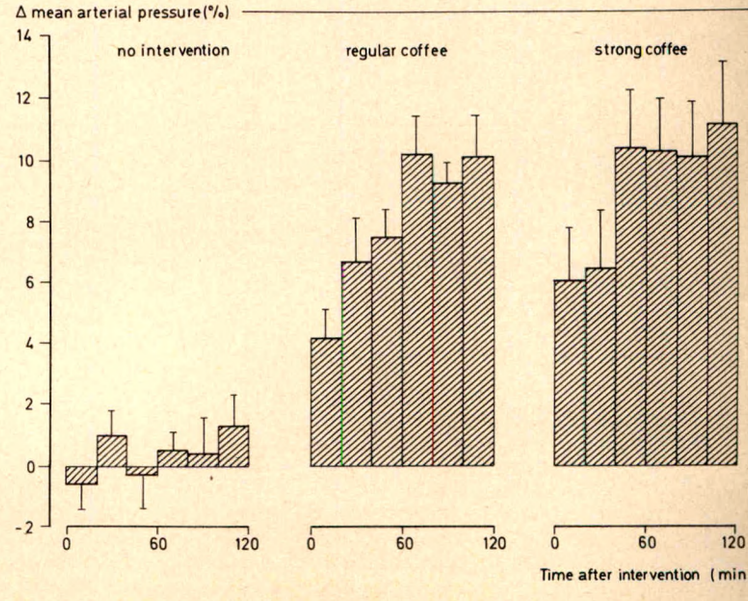

FIGURE 4. Fractional changes of mean arterial pressure for every 20-minute period after no intervention and after consumption of regular and strong coffee (mean ± standard error of the mean).

TABLE II Mean Changes in Plasma Catecholamines in the Five Tests

	NI	W	DC	RC	SC
Epinephrine (%)	75 ± 33	61 ± 41	33 ± 10	86 ± 14*	140 ± 47*
Norepinephrine (%)	−2 ± 5	6 ± 11	4 ± 8	7 ± 6	14 ± 10

* $p < 0.05$ vs decaffeinated coffee test.
All values are mean ± standard error of the mean.
Abbreviations as in Table I.

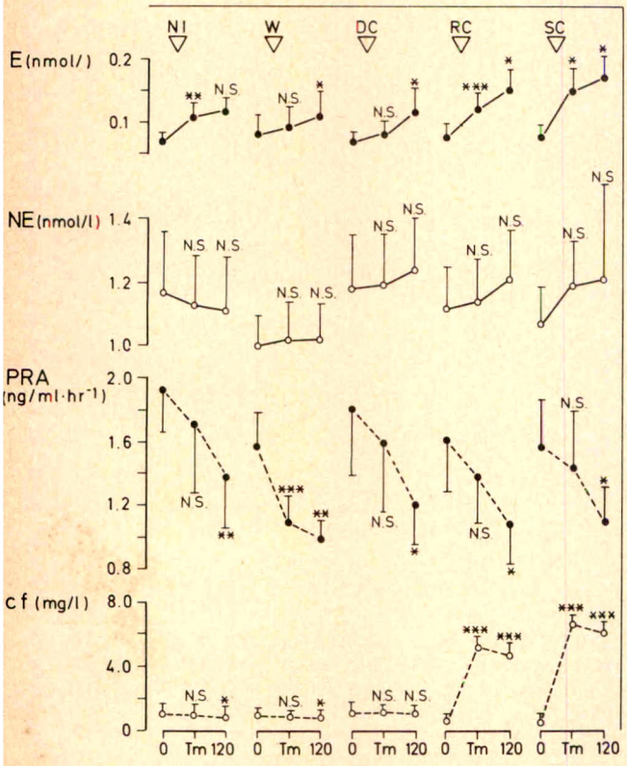

FIGURE 5. Mean (± standard error of the mean) values (n = 8) of plasma concentrations of norepinephrine (NE, E), renin (PRA) and caffeine (cf) before, at plasma peak level (Tm) and 120 minutes after no intervention (NI), consumption of water (W), decaffeinated coffee (DC), regular coffee (RC) and strong coffee (SC). **Asterisks** represent significances with respect to basal values. NS = not significant; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

plain contradictory observations reported with respect to the circulatory effects of caffeine. The evident disparity between the acute effects of caffeine and the results of epidemiologic studies, which show no association between coffee and coronary heart disease,[16–18] also has been explained by the phenomenon of tolerance.[8]

In this study we could affirm the presumption that BP increase after consumption of coffee depends on basal plasma caffeine concentration (Fig. 6). Further, the problem has been evaluated from another point of view by testing the hypothesis, that a significant BP increase will occur when abstinence of caffeine is long enough to reach low basal plasma caffeine levels. In this study we used a caffeine abstinence of 4.5 half-lives, and such periods of abstinence are likely to occur in daily life. The range of half-lives from 2 to 8.5 hours in our subjects is in close agreement with other observations,[10] and this wide range is brought about by several exogenic influences,[19,20–22] as well as by genetically determined interindividual differences.[23] Despite a significant difference between the increase in plasma caffeine levels after ingestion of regular and strong coffee, the responses of BP were similar (Fig. 4). These results agree with the observation of a flat dose-response curve with respect to the BP-increasing effect of drinking 2 to 8 cups of coffee.[24] The observed BP increase after coffee ingestion did not show any correlation with the duration of caffeine abstinence. Consequently, we conclude that drinking coffee leads to an increase in BP after caffeine abstinence for 4.5 half-lives. In a previous study, plasma caffeine levels were measured in 600 consecutive patients; in about 50% of this group, plasma caffeine

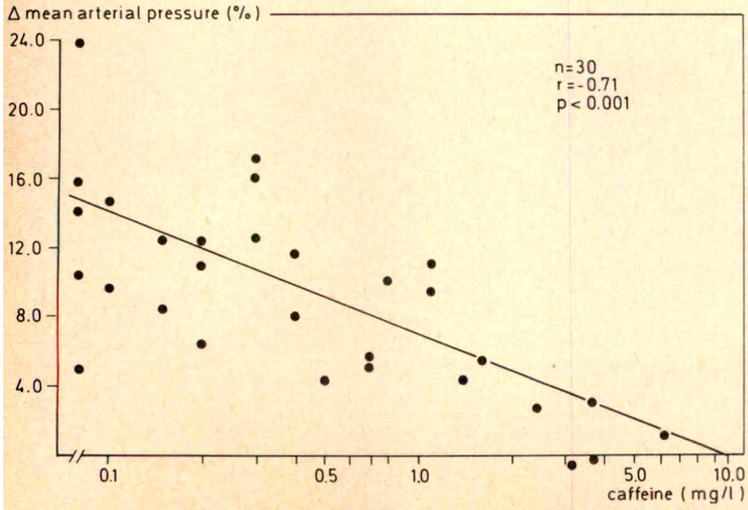

FIGURE 6. The relation between basal plasma caffeine concentration and the fractional increase in mean arterial pressure in the second hour after consumption of coffee in 30 normotensive subjects. (Δ mean arterial pressure vs ^{10}log [caffeine]).

concentration was less than 2.0 mg/liter.[25] This indicates that drinking coffee may induce an increase in BP in daily life in a considerable proportion of the population. Drinking decaffeinated coffee induced only a small increase in diastolic BP, an observation that agrees with reported data.[26]

In another study, stronger BP increases are reported after a comparable load of coffee drinking.[6] However, in that study caffeine abstinence was longer, also reflected by a lower mean basal plasma caffeine of 0.3 mg/liter. Probably, the lower BP response to coffee in this study can be traced to partial tolerance, which would disappear after longer caffeine abstinence. The complete tolerance in Robertson's study,[8] even after 15 hours of caffeine abstinence, can be explained by the extremely long mean $T^1/_2$ (10 hours) of his subjects, resulting in a mean basal plasma caffeine of 2.3 mg/liter. Ammon et al[9] also observed complete tolerance to coffee, but no plasma caffeine data were available.

Epidemiologic studies have related mean coffee consumption to BP. Because of the results of this study, we believe a more valid conclusion could be drawn if the pharmacokinetics of caffeine were taken into consideration. Additionally, epidemiologists always correct for cigarette smoking because smoking is an independent risk factor in coronary heart disease and because coffee consumption and cigarette smoking are strongly related habits.[16] Because mean $T^1/_2$ of caffeine is shorter in people who smoke,[19] our results indicate that such a correction could lead to underestimation of the relation between BP or coronary heart disease and coffee.

Decreases in heart rate did not reveal clear significant differences between the 5 tests and, therefore, an additional effect of caffeine on the decrease in heart rate could not be proved with these observations, in contrast to other reports.[5,26] The changes in forearm blood flow and forearm vascular resistance illustrate that drinking strong coffee induces a slight vasodilation in the forearm muscle when compared with beverages containing no or a very small amount of caffeine. These data are not conclusive with respect to the effect of coffee on total peripheral resistance, because caffeine could induce opposite effects in blood vessels of other organ systems.

Changes of plasma epinephrine after consumption of coffee were less striking than in former reports.[6,26] This also may be explained by partial tolerance to the effects of coffee. The decrease in plasma renin activity in all tests, including the no-intervention test, suggests that this could be the result of the circadian rhythm of plasma renin activity, because all tests were performed in the morning.[27]

From this study we conclude that drinking coffee results in an increase in BP and a possible vasodilation in forearm muscle. Plasma epinephrine levels tend to increase after coffee, whereas plasma norepinephrine and renin activity do not change. There are no differences when drinking regular or stronger coffee. Drinking water does not result in circulatory changes, whereas drinking decaffeinated coffee induces a small increase in diastolic BP when compared with no intervention. Relevant hemodynamic changes with coffee already occur after caffeine abstinence of 4.5 half-lives. In normotensive subjects there is a strong negative correlation between the coffee-induced BP increase and basal plasma caffeine concentration. The $T^1/_2$ of caffeine shows a large variation, and subjects with short $T^1/_2$ are definitely exposed to pressor responses to coffee, depending on their daily intake.

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Beta-Adrenergic Stimulation Reverses Postischemic Myocardial Dysfunction Without Producing Subsequent Functional Deterioration

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The prolonged myocardial dysfunction observed after reversible ischemia (stunned myocardium) has been postulated to result from an inability of the myocytes to replenish ATP stores. Accordingly, one would expect inotropic stimulation to result in minimal increase in contractile function, or possibly even further deterioration. To test this hypothesis, studies were performed in open-chest dogs undergoing a 15-minute occlusion of the left anterior descending coronary artery (LAD) followed by 4 hours of reperfusion. Systolic wall thickening, an index of regional myocardial function, was measured in the LAD-dependent territory with ultrasonic crystals. Thickening fraction was 20.8 ± 3.0% (mean ± standard error of the mean) under baseline conditions, decreased to −18.6 ± 1.6% during LAD occlusion, and was still severely depressed after 3 hours of reperfusion (2.6 ± 3.4%). Thickening fraction remained stable between 3 and 4 hours of reperfusion in 5 untreated control dogs. In 9 treated dogs, isoproterenol (0.1 μg/kg/min intravenously for 30 minutes starting 3 hours after reperfusion) increased thickening fraction to values (24.8 ± 4.5%) that were similar to those at baseline. Thirty minutes after discontinuation of isoproterenol administration, thickening fraction had returned to pre-isoproterenol levels. Thus, reperfused, severely depressed myocardium responds dramatically to β-adrenergic stimulation without subsequent adverse effects on function in the short-term. These findings imply that the stunned myocardium can generate ATP, and therefore do not support the view that an inability to replenish ATP stores is the cause of postischemic dysfunction. More important, this study suggests that postischemic dysfunction in humans may be effectively reversed with inotropic therapy without short-term deleterious sequelae.

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Myocardial reperfusion after a reversible ischemic insult is associated with prolonged contractile dysfunction (stunned myocardium).[1–3] Despite considerable investigative efforts, the mechanism for this phenomenon is unknown. Recent studies show that myocardial ATP levels are depressed after reperfusion and recover in parallel with contractile function.[2,4–6] Thus, the hypothesis has been advanced[2,3,5] that postischemic dysfunction may be the result of an inability of the myocardium to generate enough high-energy phosphates to sustain contractile function, possibly because of loss of adenine nucleotide precursors.[3,7]

Insights into this problem may be gained by assessing the effect of inotropic stimulation on reperfused, depressed myocardium. If, in fact, ATP stores in stunned myocardium cannot be repleted, inotropic stimuli would be expected to produce little or no increase in contractility or even further deterioration. A marked improvement in mechanical function, in contrast, would imply preserved ability to generate ATP. These results would have clinical implications, because it is unclear whether inotropic therapy can precipitate deleterious effects in patients with postischemic dysfunction. Accordingly, in the present study we evaluated the response of reperfused, depressed myocardium to

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inotropic stimulation by the β-adrenergic agonist isoproterenol. We used a well characterized[2–4] open-chest canine model in which severe myocardial dysfunction was induced by 15 minutes of coronary artery occlusion followed by reperfusion.

Methods

Experimental preparation: Mongrel dogs of either sex that weighed 15 to 30 kg were anesthetized with sodium pentobarbital (30 mg/kg intravenously [i.v.]), intubated and ventilated with room air. The chest was opened through the left fifth intercostal space and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was isolated from the surrounding tissue and encircled by a snare just distal to the first major diagonal branch.[8] A Doppler ultrasonic flow probe was placed around the artery distal to the site of occlusion. A polyethylene catheter was inserted through the left carotid artery into the aorta and was connected to a Statham P23Db pressure transducer. A high-fidelity micromanometer (Konigsberg P-7) was inserted into the left ventricular (LV) cavity through a stab incision in the apex. The first derivative of LV pressure (dP/dt) was obtained by electronic differentiation. To measure regional LV wall thickening in treated dogs, a pair of miniature (2 mm in diameter) ultrasonic crystals was positioned in the anterior LV wall in the region to be rendered ischemic. One crystal was inserted at an angle of 45° through the wall into the subendocardium and the other crystal was sutured to the epicardial surface at a site where the ultrasonic transit time was shortest.[9] Wall thickening in control dogs was measured with a 10-MHz pulsed Doppler ultrasonic crystal sutured to the epicardial surface. Theoretical and experimental validation of this probe has been reported.[10,11] Aortic pressure, LV pressure, LV dP/dt, LAD blood flow velocity, LV wall thickness and lead II of the electrocardiogram were recorded continuously throughout the study on an 8-channel, direct-writing oscillograph (Gould Brush, system 200).

Experimental protocol: The LAD was occluded with a hydraulic balloon occluder for 15 minutes and then reperfused for 4 hours. Beginning 3 hours after reperfusion, 9 dogs received a continuous infusion of isoproterenol (0.1 μg/kg/min i.v.) for 30 minutes, whereas 5 control dogs did not receive any treatment. Hemodynamic variables and LV wall thickness were measured before and during LAD occlusion, 1, 2 and 3 hours after reperfusion, at 10 and 30 minutes of isoproterenol infusion, and 30 minutes after cessation of infusion (i.e., 4 hours after reperfusion). Dogs were then killed with KCl (10 mEq i.v.). The heart was excised and sectioned from apex to base into 5 to 6 slices, which were incubated for 20 minutes in 1% triphenyl tetrazolium chloride (TTC) solution at 37°C[12] to verify the absence of infarction.

Measurement of wall thickening: In treated dogs, which were instrumented with 2 transit-time crystals, end-diastolic and end-systolic wall thicknesses were measured at the rapid upstroke of LV pressure and at peak negative LV dP/dt, respectively.[13] Percent systolic wall thickening (%WT) was calculated from the formula[14] (ESWT–EDWT)/EDWT × 100, where ESWT = end-systolic wall thickness and EDWT = end-diastolic wall thickness. In control dogs, which were instrumented with Doppler thickening crystals, %WT was calculated from the formula (ST/EDT) × 100, where ST = systolic increase in wall thickness and EDT = end-diastolic thickness estimated from the sample volume depth.[10] Percent systolic wall thickening measured by the Doppler probe correlates closely with that determined by the 2-crystal transit-time method over a wide range of values.[10,11] Measurements from at least 5 beats were averaged at each time point.

TABLE I Systemic Hemodynamics and End-Diastolic Left Ventricular Wall Thickness Before and During Left Anterior Descending Coronary Artery Occlusion and at Selected Times After Reperfusion

	Baseline	Occlusion	1 Hour	2 Hours	3 Hours	Isoproterenol 10 Min (3 h 10 min)	Isoproterenol 30 Min (3 h 30 min)	30 Min After Isoproterenol (4 h)
Treated Group (n = 9)								
Heart rate (beats/min)	147 ± 6	148 ± 6	147 ± 7	148 ± 8	148 ± 8	193 ± 8*	187 ± 8*	151 ± 8
Mean arterial pressure (mm Hg)	112 ± 4	102 ± 3	107 ± 6	112 ± 6	111 ± 6	98 ± 4	98 ± 3	107 ± 3
Peak positive LV dP/dt (mm Hg/s)	2,120 ± 208	1,890 ± 182†	1,984 ± 236	2,093 ± 167	2,016 ± 167	5,053 ± 536*	5,042 ± 560*	2,332 ± 399
End-diastolic wall thickness (mm)	8.4 ± 0.5	7.1 ± 0.5†	8.1 ± 0.6	8.1 ± 0.6	8.2 ± 0.6	8.5 ± 0.6	8.5 ± 0.6	8.2 ± 0.6
Control Group (n = 5)								
Heart rate (beats/min)	131 ± 4	138 ± 4	133 ± 9	133 ± 11	128 ± 13			130 ± 16
Mean arterial pressure (mm Hg)	116 ± 5	113 ± 4	106 ± 2	106 ± 2	106 ± 3			109 ± 2
Peak positive LV dP/dt (mm Hg/s)	2,283 ± 611	2,011 ± 414†	2,242 ± 383	2,366 ± 433	2,018 ± 254			2,002 ± 233
End-diastolic wall thickness (mm)‡	9.2 ± 0.6	7.2 ± 0.5†	8.1 ± 0.6	8.1 ± 0.6	8.1 ± 0.6			8.3 ± 0.6

* $p < 0.001$ vs 3 hours; † $p < 0.01$ vs baseline.
‡ Estimated from the depth of the Doppler sample volume.[11]
Values are mean ± standard error of the mean.
LV = left ventricular.

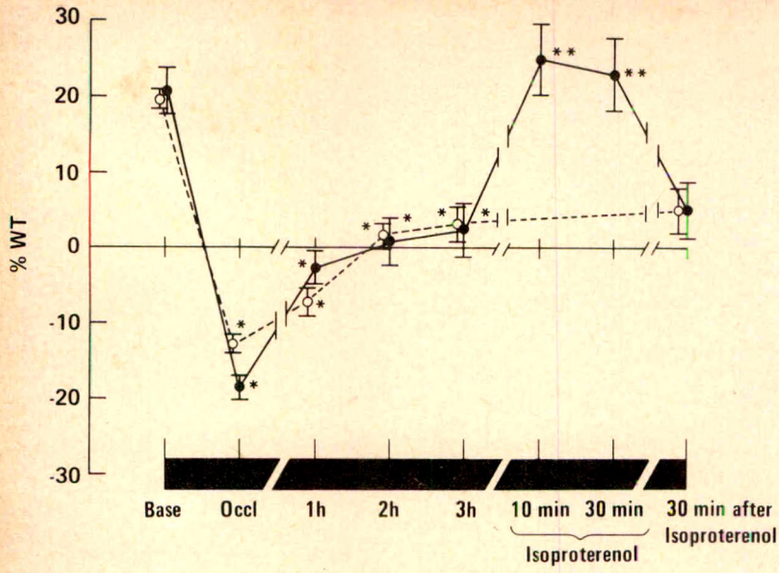

FIGURE 1. Percent systolic wall thickening (% WT) under baseline conditions (Base), during coronary occlusion (Occl), and at selected times after reperfusion. **Solid circles** with **continuous line** represent the treated group, which received isoproterenol between 3 and 3.5 hours of reperfusion; **open circles** with **dashed line** represent the control group. Wall thickening was still markedly depressed at 3 hours of reperfusion in both groups, but increased strikingly in response to isoproterenol, attaining levels slightly higher than those observed under baseline conditions, *p <0.001 vs baseline; **p <0.01 vs 3 hours.

Statistical analysis: All values are reported as mean ± standard error of the mean. Analysis of variance was used to test the differences in repeated measurements from the same dogs. If the F test showed an overall difference, comparisons between 2 time points were performed by the 2-tailed Student *t* test for paired data and the resulting p values were adjusted by Bonferroni's method.[15]

Results

Of the 18 dogs initially instrumented, 1 dog died of ventricular fibrillation during occlusion and 3 dogs died after reperfusion. The results from the remaining 14 dogs (5 control and 9 treated) form the basis of this report. TTC staining showed no evidence of irreversible damage in any of these dogs.

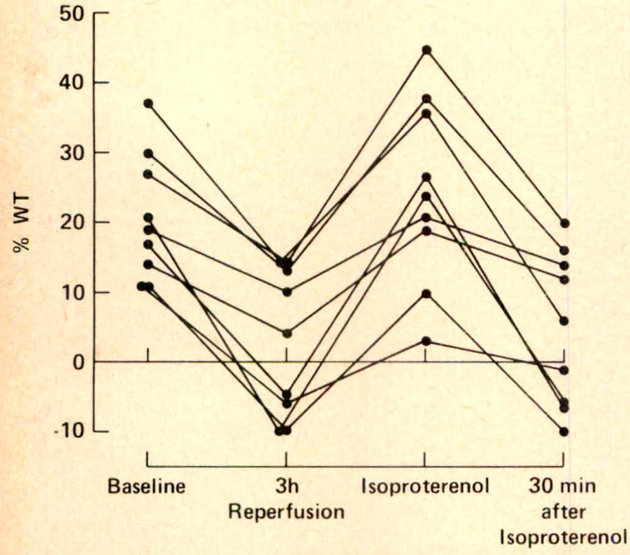

FIGURE 2. Effect of isoproterenol on percent systolic wall thickening (% WT) in individual dogs. Wall thickening values under baseline conditions, before isoproterenol (3 hours of reperfusion), 10 minutes after the start of isoproterenol infusion, and 30 minutes after cessation of infusion are shown. Isoproterenol consistently improved regional function in all dogs, including those exhibiting dyskinesia, and restored wall thickening to baseline values or above in all but 1 dog.

Systemic hemodynamics: Heart rate, mean aortic pressure and peak positive LV dP/dt values are listed in Table I. Three hours after LAD reperfusion, systemic hemodynamic values were similar to values at baseline. In the treated group, isoproterenol significantly increased heart rate and LV dP/dt ($p < 0.001$), and tended to lower aortic pressure ($p < 0.10$). These effects were no longer discernible 30 minutes after discontinuation of isoproterenol. Hemodynamic variables remained stable between 3 and 4 hours in the control group.

Regional function: In both groups, end-diastolic wall thickness decreased during LAD occlusion ($p < 0.01$), but returned to values similar to baseline after 1 hour of reperfusion (Table I). Isoproterenol produced an insignificant increase in end-diastolic wall thickness (Table I).

During LAD occlusion, systolic wall thickening was replaced by paradoxical holosystolic thinning in all dogs. After reperfusion, wall thickening remained severely depressed and at 3 hours averaged only 13.6% of the preocclusion value in the control and 12.3% in the treated group (Fig. 1). In the treated group, isoproterenol produced a dramatic increase in wall thickening, from 2.6 ± 3.4% to 24.8 ± 4.5% at 10 minutes and 23.0 ± 4.9% at 30 minutes of infusion ($p < 0.001$), values that were slightly higher than those recorded before LAD occlusion (Fig. 1). The increase was consistently observed in all dogs (Fig. 2). In the 4 dogs that still had paradoxical systolic thinning at 3 hours of reperfusion, isoproterenol induced resumption of active systolic thickening (Fig. 2). The β-adrenergic agonist restored regional contractile function to baseline levels or above in all but 1 dog (Fig. 2). An original representative recording from 1 dog is shown in Figure 3. Thirty minutes after cessation of isoproterenol infusion, wall thickening had returned to levels similar to those before infusion (Fig. 1 and 2). No significant change in wall thickening was observed between 3 and 4 hours of reperfusion in the 5 control dogs (Fig. 1).

Discussion

This study shows that reperfused, severely depressed myocardium possesses considerable functional reserve. Isoproterenol reversed postischemic dysfunction and restored wall thickening to preocclusion baseline levels (although not to the higher levels that would be expected with β-adrenergic stimulation under normal conditions). Moreover, our data show that even intense inotropic stimulation of stunned myocardium does not result in early functional deterioration after the inotropic agent is discontinued.

Our results are in agreement with those of a previous study by Mercier et al[16] showing that the administration of dopamine for 10 minutes improves the contractile function of reperfused, depressed myocardium. Mercier et al assessed segmental myocardial shortening, whereas we measured LV wall thickening. The latter method may more accurately reflect transmural myocardial function than the segment-length method because it is not affected by the variation in fiber orientation in the different layers of the LV wall.[17] Mercier et al showed that the contractile function of stunned myocardium can be greatly enhanced, but the 10-minute stimulation period may have been too short to precipitate potential deleterious sequelae. We thus extended the period of inotropic stimulation to 30 minutes. Furthermore, in order to produce intense myocardial stress, we administered large doses of isoproterenol, an extremely potent inotropic agent. It is unlikely that afterload reduction secondary to the vasodilator effects of isoproterenol contributed significantly to the enhanced contractility of stunned myocardium, because the drug produced only modest reductions in mean (from 111 ± 6 to 98 ± 3 mm Hg) and systolic (from 131 ± 6 to 126 ± 6 mm Hg) arterial pressure; furthermore, there was no significant correlation between the inotropic and hypotensive effects of isoproterenol.

Our transmural measurements of myocardial thickening do not provide information regarding the relative responses of the inner and outer layers of the LV wall to isoproterenol. Theoretically, such responses may differ. Coronary occlusion in the dog results in nonuniform transmural ischemia, with more severe flow reductions in the subendocardial than in the subepicardial layers. Recent studies from this laboratory[18] indicate that recovery of contractile function after a 15-minute coronary occlusion followed by reperfusion is also nonuniform across the LV wall, occurring more slowly in the subendocardium than in the subepicardium. Further investigations are necessary to determine whether the increased transmural myocardial thickening that is observed with inotropic stimulation reflects improved contractile performance in all layers or primarily in the less severely injured subepicardial layers.

The present study has important implications with regard to the mechanism of postischemic dysfunction. Several recent investigations[2,4–6] indicate that postischemic dysfunction is associated with myocardial ATP depletion, suggesting that the 2 phenomena may be causally related. During ischemia ATP is degraded to metabolites such as adenosine, hypoxanthine and inosine, which readily diffuse across cell membranes and are therefore washed out of the myocardium at the time of reperfusion.[3,7] Resynthesis of ATP can occur through either a slow *de novo* pathway or a faster "salvage" pathway, which involves production of adenine nucleotides from adenosine, hypoxanthine and inosine.[5] The loss of these precursors from the reperfused myocardium limits the latter pathway and is believed to account, in part, for the prolonged ATP depletion observed after reversible ischemia.[2,3,5]

If resynthesis of ATP in stunned myocardium were inherently limited, one would expect little or no response to stress, or possibly even a deterioration as a result of rapid utilization of the remaining high-energy phosphates. The striking, sustained increase in contractility observed in the present study during isoproterenol infusion and the absence of deleterious sequelae, however, clearly indicate that even severely depressed myocardium is capable of substantial ATP production, at least sufficient to support return of function to baseline levels. Hence, impaired resynthesis of ATP is not, in itself, the primary factor responsible for postischemic dysfunction. Further evidence corroborating this conclusion is provided by the finding that manipulations that attenuate ATP depletion after reversible ischemia do not result in functional improvement,[19,20] and that the severity of postischemic dysfunction does not correlate with myocardial ATP levels.[21] Recent studies from this laboratory suggest that an alternative mechanism for postischemic dysfunction may be the generation of oxygen free radicals during ischemia or reperfusion.[22] Among their many deleterious effects, these toxic oxygen metabolites cause damage to the sarcoplasmic reticulum, which may result in excitation-contraction uncoupling.[23]

Our data may have implications for numerous clinical settings in which the myocardium is exposed to transient ischemia, including acute myocardial infarction with early reperfusion (either spontaneous or induced by thrombolytic therapy), unstable or variant angina, open-heart surgery with cardioplegic arrest and cardiac transplantation. The presence of stunned myocardium

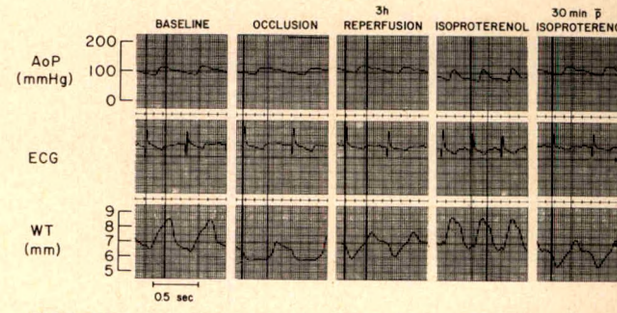

FIGURE 3. Original recordings from a dog in the treated group. Systolic wall thickening (WT) present under baseline conditions was replaced by holosystolic thinning during left anterior descending coronary artery occlusion with minimal recovery 3 hours after reperfusion. Isoproterenol markedly increased function, with resumption of active systolic thickening. Thirty minutes after isoproterenol was discontinued (30 min $\bar{p}$ isoproterenol), wall thickening was similar to that observed before isoproterenol. AoP = aortic pressure; ECG = electrocardiogram. **Vertical lines** indicate beginning and end of systole.

in these settings is suggested by several recent observations,[3,24–26] and may be an important factor precipitating LV failure. If applicable to man, our results indicate that postischemic dysfunction can be effectively reversed with inotropic therapy without short-term deleterious sequelae. Further studies, however, are needed to determine whether such inotropic stimulation adversely affects the recovery of stunned myocardium in the long term.

Acknowledgment: The expert secretarial assistance of Lisa Gearinger is gratefully acknowledged.

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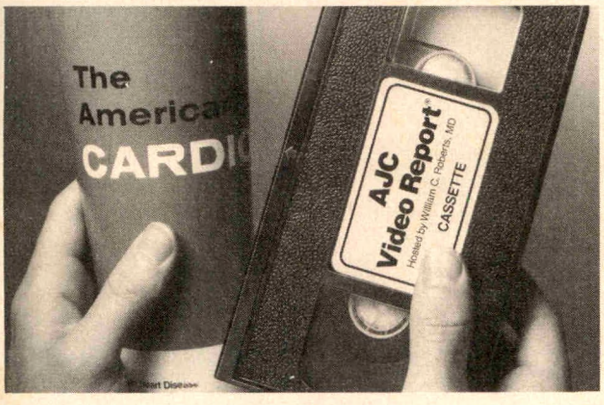

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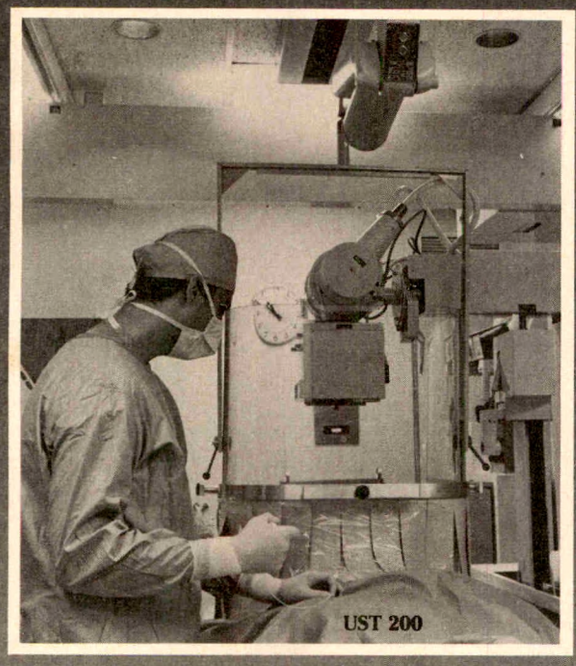

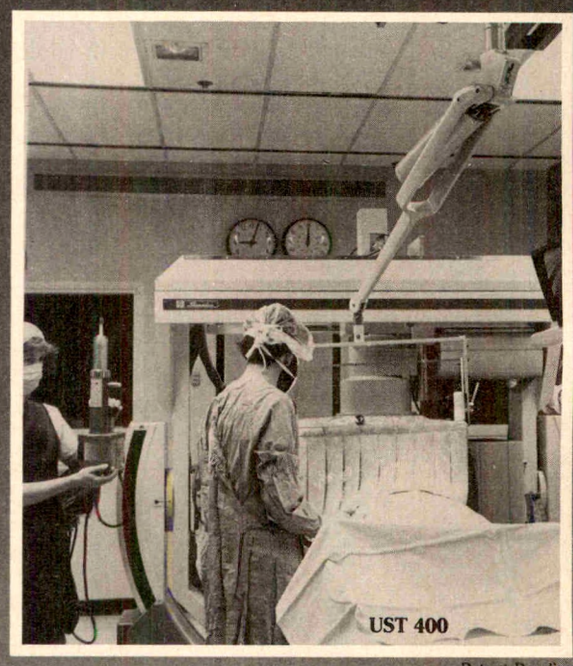

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Myocardial Kinetics of Thallium-201 After Stress in Normal and Perfusion-Reduced Canine Myocardium

ROBERT D. OKADA, MD

Despite the emerging use of quantitative computer programs for assessing myocardial thallium uptake and clearance after exercise, little is known about the kinetics of thallium after exercise stress. Accordingly, 11 mongrel dogs with experimental left anterior descending coronary stenoses were given thallium during norepinephrine infusion to simulate exercise. The infusion was discontinued and thallium activity was monitored regionally using miniature radiation detectors for 3 hours. Heart rate, arterial pressure and double product all increased significantly during norepinephrine infusion. The mean fractional myocardial thallium clearance was lower (0.47 ± 0.03 [± standard error of the mean]) for the stenosis zone than for the no-stenosis zone (0.57 ± 0.03) ($p < 0.0001$). The stress blood flow ratio (stenosis/no-stenosis zone = 0.27 ± 0.06) was significantly lower than the final thallium activity ratio (0.68 ± 0.07) ($p < 0.001$), consistent with thallium redistribution occurring over the 3-hour period. Myocardial thallium activity in the stenosis zone peaked in a mean of 2.2 minutes, then washed out biexponentially with a final decay constant of 0.0035 ± 0.0005 min^{-1}. Myocardial thallium activity in the no-stenosis zone peaked within 1 minute in all dogs, then washed out biexponentially, with a final decay constant of 0.0043 ± 0.0003 ($p < 0.001$ compared with stenosis zone). In conclusion, fractional clearance of thallium can differentiate myocardium distal to a coronary artery stenosis from that supplied by a normal coronary vessel.

(Am J Cardiol 1985;56:969–973)

Thallium-201 imaging in conjunction with exercise electrocardiography is widely used for the diagnosis of coronary artery disease. Studies have shown an improved diagnostic accuracy for the thallium study compared with exercise electrocardiography alone.[1] Thallium redistribution—the resolution on delayed images of a defect observed on initial post-stress images—has been used as an indication of stress-induced ischemia as opposed to scar.[2] Quantitative computer techniques were recently described for analyzing the initial uptake and subsequent clearance of thallium from the myocardium.[3–11] Therefore, it is important to understand the kinetics of thallium uptake and clearance from ischemic and normal myocardium after thallium administration during stress. Normal myocardial thallium clearance rates are difficult to determine from patient studies, because background can be difficult to subtract accurately. Therefore, miniature implantable cadmium telluride radiation detectors were developed.[12] These detectors permit continuous monitoring of thallium activity in experimental models without the need for background correction. In the present study these miniature radiation detectors were used to study thallium kinetics after stress in myocardium supplied by stenotic and normal coronary arteries.

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Methods

Canine preparation: Eleven adult mongrel dogs (mean weight 20 kg, range 17 to 23) were studied. The canine preparation has been reported.[13] Electrocardiographic lead II and pressures (P23Db transducers, Gould Inc.) were monitored continuously throughout the experiment and recorded on paper with a Hewlett-Packard recorder (model 7788A). Samples of arterial blood were drawn frequently to assess pH, P_{O_2} and P_{CO_2}. Appropriate adjustments were made to maintain values in the physiologic range (pH 7.35 to 7.45 and P_{CO_2} 30 to 40 mm Hg). Arterial P_{O_2} was maintained between 100 and 150 mm Hg throughout the experiment.

A miniature cadmium telluride radiation detector attached to a modified arterial clamp was inserted through the left ventricular apex, positioned against the posterior wall endocardium, and used for on-line monitoring of thallium-201 activity distal to the balloon occluder (Fig. 1). A similar detector was positioned against the left ventricular anterior wall endocardium. The endocardial position for the detectors was chosen so that monitored activity would be less affected by activity from the opposite wall and the blood pool. The anterior wall detector was positioned to face through the open thoracotomy, thereby further reducing background activity. A lead sheet (1/8 inch) was placed between the posterior wall and the pericardium to further reduce background activity from this probe. The physical characteristics of the cadmium telluride probes have been reported.[6] The probes were connected via preamplifiers to a multichannel analyzer (Series 30, Canberra Industries), which allowed continuous moni-

TABLE I Hemodynamic Data

Dog	HR (beats/min)			MAP (mm Hg)			RPP (Systolic)		
	R	S	E	R	S	E	R	S	E
1	180	250	190	100	185	95	19,800	52,500	20,900
2	150	200	170	85	180	85	16,500	40,000	17,000
3	185	220	190	90	160	95	18,500	36,000	20,900
4	200	240	200	98	160	95	24,000	54,000	20,000
5	130	189	130	70	150	75	13,010	30,240	11,700
6	200	230	200	110	140	100	26,000	39,100	28,000
7	160	180	160	80	110	100	14,400	22,500	15,000
8	170	190	170	100	140	90	20,400	38,000	18,700
9	200	220	200	110	165	100	26,000	44,000	24,000
10	150	190	140	90	125	90	15,000	19,026	14,000
11	180	200	180	130	250	135	25,200	58,000	26,500
Mean ± SEM		R 173 ± 7			97 ± 5			19,892 ± 4,845	
		S 209 ± 7			160 ± 10			31,028 ± 13,927	
		E 175 ± 7			96 ± 4			19,700 ± 5,132	

CO = cardiac output; E = end of experiment; HR = heart rate; LAD = left anterior descending coronary artery; LAP = left atrial pressure; MAP = mean arterial pressure; ND = not done; PAP = pulmonary artery pressure; R = rest; RPP = rate-pressure product; S = stress; SEM = standard error of the mean; Sono = sonomicrometry.

toring and display of thallium-201 activity in the 2 regions. Sonomicrometer transducer crystals (3 mm in diameter) were attached to both arms of each arterial clamp and connected to a sonomicrometer (model NI-202-4R, Norland Instruments) to determine wall thickness.[14]

Experimental protocol (Fig. 2): Using the electromagnetic flow probes as guides, the balloon occluder was inflated to create resting flow ratios (left anterior descending/left circumflex zones) ranging from 0.95 to 0.40 for the 11 dogs. After a 30-minute stabilization period, baseline hemodynamic values were recorded. These measurements included heart rate, cardiac output, sonomicrometer-determined wall thickness, and arterial, left atrial, pulmonary arterial and distal left anterior descending coronary arterial pressures. Regional myocardial blood flow was determined by the administration of 4.5 million tin-113-labeled, 15- to 17-μ microspheres (30 μCi total activity) into the left atrium. Arterial reference blood samples were collected for 2 minutes after the microsphere injection.

An infusion of norepinephrine was then started into the right atrium (8 mg in 250 ml of saline solution). The infusion rate was increased, aiming for a target arterial systolic blood pressure of 200 mm Hg, because this level is the maximal response in untethered dogs.[15] The infusion was continued for 4 minutes. Thallium-201, 1.0 mCi, was then administered into the second venous catheter. Simultaneously, regional myocardial blood flow was determined by administration of 4.5 million niobium-95-labeled, 15- to 17-μ microspheres (30 μCi total activity) into the left atrium. Arterial reference blood samples were collected for 2 minutes. To measure blood thallium activity over time, 1-ml arterial blood samples were collected at 2, 4, 6, 8, 10, 20, 30, 60, 90, 120, 180 and 240 min-

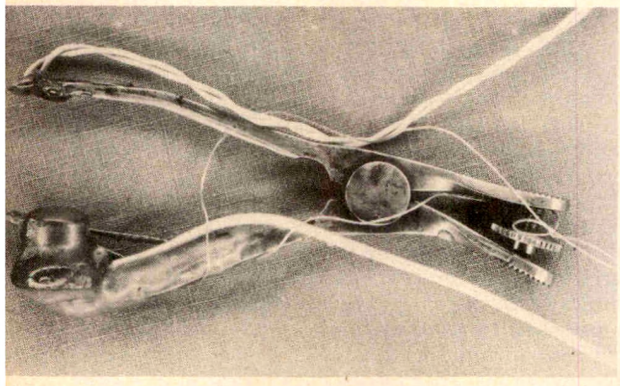

FIGURE 1. Miniature radiation detector assembly. The miniature radiation detector is mounted on the end of a modified vascular clamp.

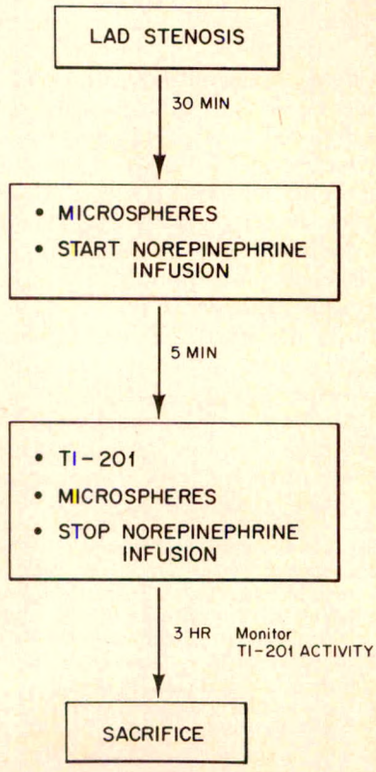

FIGURE 2. Experimental protocol. LAD = left anterior descending coronary artery.

CO (liters/min)			Mean LAP (mm Hg)			Mean PAP (mm Hg)			Mean Distal LAD Pressure (mm Hg)			Myocardial Blood Flow (ml/min/g)						
												Rest		Stress		LAD Sono		
R	S	E	R	S	E	R	S	E	R	S	E	Stenosis	No Stenosis	Stenosis	No Stenosis	R	S	E
2.3	2.9	2.2	13	14	2	27	16	9		ND		0.50	1.05	0.58	2.00	6.5	6.0	5.9
3.0	3.9	2.7	11	16	9	27	40	25		ND		1.01	1.25	0.96	2.20	8.7	9.8	8.5
3.6	4.5	3.6	3	25	7	15	32	18	85	60	50	1.08	1.54	0.88	3.95	12.5	12.5	12.5
2.3	3.7	2.3	9	20	4	20	35	26	45	60	25	0.38	1.32	0.77	4.35	9.3	10.4	9.3
3.1	6.2	3.0	6	18	6	12	32	21	25	35	21	0.38	1.33	1.25	7.03	6.9	6.2	6.4
	ND		6	6	4	9	9	9	76	65	70	1.90	1.88	2.48	7.13	11.6	11.0	11.0
3.3	4.1	2.3	2	6	3		ND		45	45	40	0.54	0.87	0.85	5.13	10.1	10.2	10.4
2.4	8.0	2.9	3	5	3	7	19	7	45	45	45	0.72	1.20	1.00	4.02	7.0	9.0	7.9
4.0	6.0	3.6	8	10	8	33	36	33	35	35	40	0.41	2.37	0.44	7.41	9.9	9.6	9.6
2.0	3.9	2.0	4	6	4	17	23	17	40	40	40	1.11	1.06	3.16	4.61	10.4	10.5	10.5
2.4	4.0	2.5		ND		10	12	8	70	50	50	0.71	0.84	0.35	10.80	10.1	10.7	10.9
R 2.8 ± 0.2			R 6.5 ± 1.1			R 17 ± 3			R 51 ± 6			0.80 ±0.13	1.33 ±0.13	1.15 ±0.25	5.33 ±0.74	R 9.3 ± 0.5		
S 4.7 ± 0.4			S 12.6 ± 2.1			S 25 ± 3			S 48 ± 3							S 9.6 ± 0.5		
E 2.7 ± 0.2			E 5.0 ± 0.7			E 17 ± 3			E 42 ± 5							E 9.4 ± 0.6		

utes after thallium injection. One minute after the thallium injection, the norepinephrine infusion was stopped. Miniature radiation detector probe counts were then monitored continuously in 1-minute intervals over the following 180 minutes. Heart rate, cardiac output, sonomicrometer-determined wall thickness, and arterial, left atrial, pulmonary arterial and distal left anterior descending coronary arterial pressures were determined frequently. At the end of the 180-minute period, regional myocardial blood flow was determined a last time by administration of scandium-46-labeled microspheres into the left atrium. The dog was then killed and myocardial and blood samples were counted in a well counter as previously reported.[13]

Data analysis: The 3-hour fractional myocardial thallium clearance was calculated from the probe activities at the beginning (first minute values) and end of the 180-minute monitoring period. The 3-hour fractional myocardial thallium clearance for the anterior wall (balloon stenosis zone) was compared to that for the posterior wall (no balloon stenosis zone). The stress regional myocardial blood flow ratio (stenosis/no stenosis) as determined by microspheres was compared with the final thallium activity ratio as determined in the well counter. A greater final thallium ratio than stress blood flow ratio was considered evidence of thallium redistribution. Myocardial and blood time-activity curves were also analyzed using a computer-assisted, nonlinear, least-squares estimation of the decay constant λ (min^{-1}). Curves were best fit to either a monoexponential, biexponential or triexponential fit. In the case of a triexponential fit, λ_1 was the initial decay constant, λ_2 the intermediate decay constant and λ_3 the final decay constant.

Values are mean ± standard error of the mean. Differences between rest and stress hemodynamic values and between stenosis and no stenosis myocardial zones were analyzed by a paired *t* test.

Results

Hemodynamic data (Table I): Heart rate, mean arterial pressure, and double product all increased significantly during norepinephrine infusion (all $p < 0.0001$). Heart rate, arterial pressure and double product were not significantly different from baseline values at the end of the study. Cardiac output and mean left atrial, pulmonary arterial and distal left anterior descending coronary arterial pressures also increased significantly during norepinephrine stress (all $p < 0.0001$) and were unchanged from baseline values at the end of the study. Sonomicrometer-determined mean myocardial wall thickness did not change during the experiment.

Regional myocardial blood flow was significantly lower in the stenosis zone (0.80 ± 0.13 ml/min/g) than in the no-stenosis zone (1.33 ± 0.13 ml/min/g) at rest ($p < 0.001$). Blood flow in the stenosis zone increased, but not significantly, during norepinephrine infusion. Flow in the no-stenosis zone increased significantly, to 5.33 ± 0.74 ml/min/g, during norepinephrine infusion ($p < 0.0001$).

Thallium clearance data: The no-stenosis and stenosis zone myocardial thallium clearance curves for 1 dog (dog 5) are shown in Figure 3. Fractional myocardial thallium clearance was 0.61 for the no-stenosis

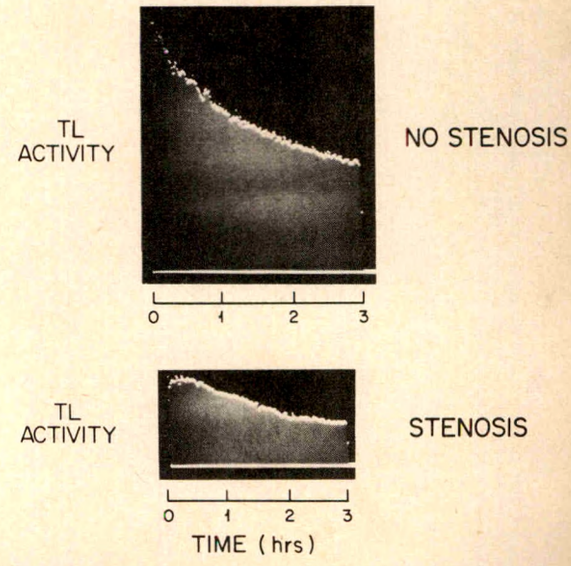

FIGURE 3. Representative probe-determined myocardial thallium (TL) clearance curves after norepinephrine for the no-stenosis and stenosis zones.

TABLE II Myocardial and Blood Thallium Washout Data

Dog	Fractional TI Washout		Time to Peak TI Activity (min)		Stress Blood Flow Ratio	Final TI Ratio	Blood TI Decay Constant			Myocardial Decay Constant λ			
	Stenosis	No Stenosis	Stenosis	No Stenosis	Stenosis	No Stenosis	λ_1	λ_2	λ_3	Stenosis λ_1	Stenosis λ_2	No Stenosis λ_1	No Stenosis λ_2
1	0.38	0.50	1	1	0.29	0.34	0.2780	0.0729	0.0072	0.0691	0.0027	0.0417	0.0033
2	0.42	0.57	2	1	0.44	0.71	0.7214	0.2843	0.0072	0.2475	0.0037	0.2525	0.0048
3	0.61	0.68	1	1	0.22	0.60	0.7820	0.7650	0.0081	0.0612	0.0056	0.1335	0.0064
4	0.54	0.57	1	1	0.18	0.49	0.7618	0.2811	0.0036	0.1522	0.0038	0.1136	0.0044
5	0.49	0.61	7	1	0.18	0.54	0.7717	0.2638	0.0077	0.0498	0.0023	0.0898	0.0030
6	0.58	0.63	1	1	0.35	0.93	0.3181	0.1000	0.0031	0.0619	0.0039	0.0092	0.0061
7	0.51	0.65	5	1	0.17	0.84	0.5437	0.1039	0.0049	0.0091	0.0072	0.0142	0.0050
8	0.48	0.59	1	1	0.25	0.89	0.7517	0.2971	0.0033	0.1376	0.0029	0.2085	0.0040
9	0.19	0.32	1	1	0.06	0.68	0.2856	0.1000	0.0042	0.1411	0.0037	0.0579	0.0042
10	0.43	0.56	1	1	0.76	1.03	0.5400	0.3551	0.0054	0.1511	0.0020	0.1528	0.0036
11	0.45	0.58	4	1	0.03	0.39	0.7081	0.2753	0.0063	0.0127	0.0007	0.0298	0.0027
Mean	0.47	0.57	2.2	1.0	0.27	0.68	0.5875	0.2615	0.0055	0.0994	0.0035	0.1003	0.0043
±SEM	±0.03	±0.03	±0.006		±0.06	±0.07	±0.0600	±0.0610	±0.0008	±0.0218	±0.0005	±0.0232	±0.0003

SEM = standard error of the mean; TI = thallium.

zone and 0.49 for the stenosis zone. Time to peak thallium activity was 1 minute for the no-stenosis zone and 7 minutes for the stenosis zone.

Table II lists the myocardial and blood thallium washout data for the 11 dogs. The mean fractional myocardial thallium clearance was significantly lower (0.47 ± 0.03) for the stenosis zone than the no-stenosis zone (0.57 ± 0.03) ($p < 0.0001$). The stress blood flow ratio (stenosis/no-stenosis zone = 0.27 ± 0.06) was significantly lower than the final thallium activity ratio (0.68 ± 0.07) ($p < 0.001$), consistent with thallium redistribution occurring between the time of thallium injection and 3 hours later.

Myocardial thallium activity in the stenosis zone peaked in a mean of 2.2 ± 0.6 minutes, then washed out biexponentially with an early mean decay constant of 0.0994 ± 0.0218 min^{-1} and a final decay constant of 0.0035 ± 0.0005 min^{-1}. Myocardial thallium activity in the no-stenosis zone peaked within 1 minute in all dogs, then washed out biexponentially with an early decay constant of 0.1003 ± 0.0232 min^{-1} and a final decay constant of 0.0043 ± 0.0003 min^{-1} ($p < 0.001$ vs stenosis zone). Blood thallium activity cleared triexponentially.

Discussion

Exercise thallium imaging is widely used to evaluate patients with chest pain. Thallium defects on initial postexercise images can represent either scar or ischemia. However, filling in of the defect, so-called thallium redistribution, is believed to differentiate ischemia from scar. For the most part, thallium images are interpreted qualitatively. Considerable training and experience is required to accurately interpret these images. Furthermore, there is considerable observer variance in the interpretations.[16] To overcome these shortcomings and in an attempt to improve the diagnostic accuracy, quantitative computer programs have been developed for interpreting serial patient thallium studies.[3–11] Normal limit profiles have been established for clearance based on studies in subjects with low probability for coronary disease. Berger et al,[11] using both distribution and clearance (absence of any washout) criteria, reported a sensitivity of 91% and specificity of 90%. Wackers et al[8] found that clearance was "almost uniform" in all myocardial segments. These investigators reported a sensitivity 89% and specificity of 95% for combined distribution and clearance criteria. Garcia and associates[9] detected coronary disease with clearance criteria alone in 2 of 20 patients. They found that 33 of 46 patients (72%) with "diffuse slow washout" of thallium had 3-vessel or left main coronary artery disease.[6] They also detected an additional 14% of diseased vascular distributions using clearance criteria.[7]

In the present study, exercise was simulated using a norepinephrine infusion. Mean heart rate, blood pressure and double product were all significantly increased by the norepinephrine infusion. However, differences do exist between this model and true exercise. With true exercise, blood flow and, thus, thallium delivery and uptake are increased in the large skeletal muscles. Therefore, although first-pass myocardial thallium uptake is the same, subsequent myocardial

uptake may be less with true exercise. Furthermore, true exercise usually produces a greater heart rate response and lesser blood pressure response compared with the norepinephrine model.

The present study demonstrates a reduced fractional thallium clearance rate from myocardium supplied by a stenosed coronary artery, when tracer was administered during exercise simulation using norepinephrine. Thus, these findings agree with clinical observations.[3–11] Whereas normally perfused myocardium showed a mean fractional clearance rate of 0.57 over 3 hours, all 11 dogs demonstrated reduced clearance rates distal to coronary stenoses. However, the normal value for fractional 3-hour clearance ranged from 0.32 to 0.68. Thus, the determinants of normal myocardial thallium clearance are probably multifactorial. Llaurado et al[17] stressed male rats by forced swimming for 2 hours, after which thallium was administered intravenously. They found a 27% clearance of thallium from normal myocardium between 30 and 180 minutes after administration. The differences between these results and the results of the present study may be in the lack of the first 30 minutes of clearance data in their study.

The mechanism of reduced thallium clearance from myocardium distal to a coronary stenosis after norepinephrine is unclear. However, neither transient nor persistent ischemia after normal myocardial thallium loading have an effect on clearance rates.[18,19] Thus, it is unlikely that persistent ischemia over the 3-hour redistribution period is the cause of reduced clearance from the stenosis-zone myocardium. Furthermore, because the effects of norepinephrine on the no-stenosis-zone myocardium are short-lived after the drug is discontinued, it is unlikely that persistent hyperemia in this zone is causing a relatively slowed clearance from the stenosis zone. Thus, the most likely cause for the slowed clearance from the stenosis zone is the difference in initial thallium uptake during the norepinephrine infusion. Compared with the normal zone, a lower initial thallium concentration in the stenosis zone would provide a smaller gradient between this zone and the blood, and this should reduce clearance.

The present study confirms that thallium redistribution (thallium heterogeneity resolution over time) occurs after exercise in viable myocardium distal to a coronary stenosis. The mechanism of thallium redistribution in the exercise stimulation model was faster clearance of tracer from normal thallium compared with the clearance from myocardium distal to a stenosis. The mechanism is similar to that observed after dipyridamole.[13] This mechanism is different from that observed in transient or persistent ischemia resting dog models. Here, thallium redistribution is a result of clearance of tracer from normal myocardium and slow accumulation in ischemic myocardium.[20–24] Using an occlusion model with release of the occlusion after thallium administration, the initial defect rapidly resolves.[22] However, even with persistent stenosis, significant thallium redistribution occurs over 4 hours.[20] Gerry et al[25] also observed a flow-independent component to thallium redistribution in dogs with circumflex coronary artery stenoses undergoing either 20 or 120 minutes of atrial pacing. Redistribution occurred despite the continued presence of pacing-induced reduced flow in the circumflex-perfused endocardial tissue. Llaurado et al[26] showed that the delayed myocardial uptake of thallium is not a result of reintroduction of tracer into the blood from other body organs.

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Relation of Myocardial Salvage to Size of Myocardium at Risk in Dogs

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Infarct size varies in untreated animals subjected to coronary artery occlusion at the same anatomic site. The relation between the hypoperfused zone and the magnitude of myocardial salvage when different pharmacologic interventions are used remains to be established. Thus, in 95 anesthetized dogs, 1 minute after left anterior descending coronary occlusion, technetium-99m-labeled albumin microspheres (8 mCi) were injected into left atrium for the assessment of the hypoperfused zone. Fifteen minutes after coronary occlusion 42 dogs were randomized into a control group and 53 into a treated group. In the treated group, 6 dogs received nifedipine, 0.35 μg/kg followed by 2.4 μg/kg/hour; 7 received diltiazem, 0.2 mg/kg followed by 0.9 mg/kg/hour; 13 received bepridil, 2.5 mg/kg; 9 received cytochrome C, 2.5 mg/kg; 8 received rutosides, 200 mg/kg; and 10 received nifedipine plus cytochrome C. All drugs were administered intravenously. At 6 hours the dogs were killed and their hearts were cut into 3-mm-thick slices. Infarct size was determined by triphenyltetrazolium chloride staining; the hypoperfused zone was delineated by autoradiography. The dogs were retrospectively subgrouped as follows: those with small hypoperfused zones, i.e., less than 15% of the left ventricle (controls n = 8, treated n = 7) and those with large hypoperfused zones, i.e., more than 15% of the left ventricle (controls n = 34, treated n = 46). In dogs with large hypoperfused zones, treatment salvaged 42 ± 3% of the myocardium destined to undergo necrosis, whereas in those with small hypoperfused zones 78 ± 10% of myocardium was salvaged ($p < 0.001$). A close inverse correlation between the hypoperfused zone and infarct size reduction was found in all treated dogs. In conclusion, more striking salvage of ischemic myocardium was observed in dogs with a small area at risk when different interventions were used after coronary artery occlusion. Thus, the initial size of the hypoperfused zone is an important determinant of the effectiveness of various pharmacologic treatments in reducing infarct size.

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Coronary artery occlusion at the same anatomic site results in significant variation in subsequent infarct size.[1] This variability is not related to changes in the major determinants of myocardial oxygen consumption, but rather, is dependent on the amount of myocardium supplied by an occluded artery, i.e., the area at risk.[1] Several investigators[1–4] have shown a close linear correlation between the size of the area at risk and subsequent necrosis in untreated animals. Therefore, the myocardium at risk is an important predictor of infarct size. Several pharmacologic interventions have been described[3,5–8] that reduce the area at risk that evolves to necrosis; thus, it is pertinent to assess whether the effectiveness of these interventions is modified by the initial area at risk. A preliminary study with methoxyverapamil[8] revealed that the drug is more effective in reducing infarct size in dogs with a small area at risk than in those with large area at risk. However, whether these findings with methoxy-verapamil are more universally applicable when other interventions are used to reduce infarct size is not known. The aim of this study was to assess the relation between the initial area at risk for infarction and the magnitude of reduction of infarct size using various pharmacologic interventions.

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Methods

Animal preparation: Ninety-five dogs were anesthetized with sodium pentobarbital, 20 mg/kg intravenously, intubated endotracheally and ventilated with room air using a volume respirator (Harvard Apparatus). Systemic arterial pressure (Statham P23Db pressure transducer) and electrocardiographic lead aVF were recorded continuously throughout the 6-hour experiments on a polygraph (Gould Instruments). A thoracotomy was performed through the fifth intercostal space and the left anterior descending coronary artery was permanently occluded proximal to the first diagonal branch for 6 hours.

Experimental protocol: One minute after coronary occlusion, 2×10^6 (8 mCi) technetium-99m-labeled albumin microspheres, 20 μm in diameter, (3M Co.) were injected into

the left atrium for the subsequent determination of the hypoperfused zone i.e., area at risk for infarction. At 15 minutes after coronary occlusion, 42 dogs were randomized to a control group and 53 to a treated group. Dogs in the treated group received various drugs intravenously: 6 received nifedipine, 0.35 μg/kg as a loading dose followed by 2.4 μg/kg/hour; 7 received diltiazem, 0.2 mg/kg as a loading dose followed by 0.9 mg/kg/hour; 13 received bepridil, 2.5 mg/kg; 9 received cytochrome C, 2.5 mg/kg; 8 received rutosides, 200 mg/kg; and 10 received nifedipine in combination with cytochrome C. Six hours after occlusion, the dogs were killed with an intravenous injection of potassium chloride and their hearts were excised. The left ventricles were then frozen at −70°C and cut into 3-mm-thick slices from the apex to the site of occlusion. Retrospectively, all dogs were arbitrarily separated into groups according to the initial area at risk: those with hypoperfused zones less than 15% of the left ventricle (controls n = 8, treated n = 7); and those with hypoperfused zones more than 15% of the left ventricle (controls n = 34, treated n = 46). All interventions were represented in both groups i.e., with large and small hypoperfused zone, respectively.

Infarct size measurements: To assess the extent of myocardial infarction, the slices were incubated in a 1.5% solution of triphenyltetrazolium chloride (Sigma Chemicals) for 10 minutes at 37°C. The reaction was stopped by rinsing with a 10% solution of formaldehyde, which enhances the red color of the normal myocardium contrasting with the pale yellow of the damaged tissue.[9] The normal and necrotic areas were then planimetered (Apple II computer). The extent of the hypoperfused zone was determined on the same slices. The slices were placed on radiographic films (Cronex 4 E.I. DuPont) and autoradiographed for 13 hours. To clearly identify their borders, soft radiographs (i.e., 25 KvP 100MAS) were also obtained and superimposed on the autoradiographs. The contours of the slices and the "cold spots"—areas of hypoperfusion—were delineated on transparent plastic sheets and planimetered (Apple II computer).

In each dog the following variables were calculated: (1) Percent of left ventricle that showed myocardial necrosis. This zone defined the infarct size. (2) Percent of left ventricle that was initially hypoperfused as determined by autoradiography ("cold spot"), and defined the hypoperfused zone. (3) Percent of the hypoperfused zone that evolved to infarction. This was calculated by dividing infarct size by the hypoperfused zone and multiplying by 100, and was used to examine whether the intervention was effective in reducing myocardial damage. (4) Effectiveness of the interventions was assessed by calculating reduction in the infarct size/hypoperfused zone ratio compared with the control group. Furthermore, percent reduction in infarct size was examined as a continuous function of the hypoperfused zone.

Statistical analysis: The results were expressed as mean ± standard error of the mean. A Student unpaired *t* test was used for comparisons between the control and treated groups. A p value <0.05 was considered significant.

Results

To verify whether the control and treated groups were comparable before intervention, heart rate and mean arterial pressure were analyzed. Accordingly, 15 minutes after coronary artery occlusion, i.e., after randomization but before the interventions were begun, heart rate was 133 ± 5 and 118 ± 3 beats/min in the control and treated groups, respectively (difference not significant [NS]). Mean arterial pressure at 15 minutes after coronary occlusion was 102 ± 4 and 99 ± 4 mm Hg (NS) in the control and treated groups, respectively.

Analysis of the extent of myocardial damage: The hypoperfused zone was 23 ± 1% of the left ventricle in the control group (n = 42) and 25 ± 1% in the treated group (n = 53) (NS). Infarct size was 21 ± 1% of the left ventricle in the control group and 14 ± 2% in the treated group (p <0.005). In the control group, an average of 92 ± 1% of the hypoperfused zone evolved to infarction, whereas in the treated group 50 ± 3% evolved to infarction, (p <0.001), indicating significant salvage of ischemic myocardium (Fig. 1).

Relation between size of the hypoperfused zone and myocardial salvage: When dogs were separated into groups according to initial risk area, 20 ± 9% of the hypoperfused zone evolved to infarction in dogs receiving treatment when the hypoperfused zone was less than 15% of the left ventricle (p <0.001 vs respective controls) and 54 ± 3% in dogs when the hypoperfused zone was more than 15% of the left ventricle (p <0.001 vs respective controls) (Fig. 2). The infarct size/hypoperfused zone ratio was 90 ± 1% and 93 ± 2% in controls with the hypoperfused zone less than 15% of the left

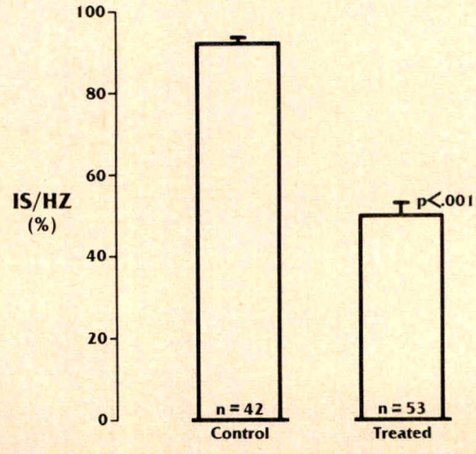

FIGURE 1. Percent of the hypoperfused zone (HZ) that evolved to necrosis, i.e., ratio of infarct size (IS) to HZ, in the control and treated groups, regardless of the initial size of the HZ. Values are mean ± standard error of the mean.

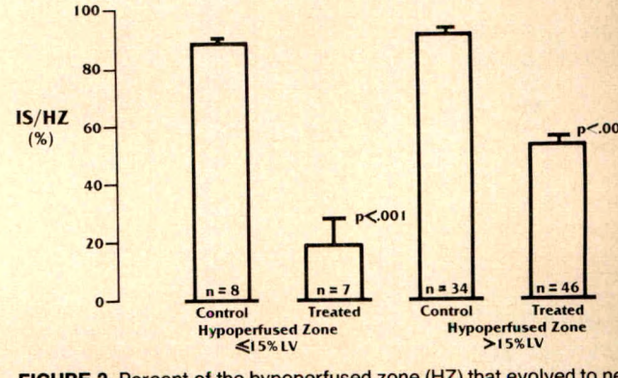

FIGURE 2. Percent of the hypoperfused zone (HZ) that evolved to necrosis, i.e., ratio of infarct size (IS) to HZ, with respect to the initial size of the HZ. Values are mean ± standard error of the mean. LV = left ventricle.

ventricle and the hypoperfused zone more than 15% of the left ventricle, respectively (NS) (Fig. 2).

Myocardial salvage as measured by reduction of the infarct size/hypoperfused zone ratio in the 2 treated groups is shown in Figure 3. In dogs with a hypoperfused zone more than 15% of the left ventricle treatment salvaged 42 ± 3% of the myocardium destined to undergo necrosis, whereas in those with the hypoperfused zone less than 15% of the left ventricle significantly more myocardium was salvaged: 78 ± 10% ($p < 0.001$). When infarct size reduction in the treated groups was analyzed as a function of the risk area (Fig. 4), a close inverse correlation was found [infarct size reduction (percent) = 127.52 − 3.51 (hypoperfused zone); n = 53, r = −0.74].

Hemodynamics: Heart rate measured at 15 minutes, 3 hours and 6 hours after coronary occlusion was 124 ± 16, 94 ± 5 and 119 ± 16 beats/min in the treated group with the hypoperfused zone less than 15% of the left ventricle and 117 ± 3, 108 ± 3 and 112 ± 4 beats/min in the treated group with a hypoperfused zone greater than 15% of the left ventricle (NS). Mean arterial pressure at 15 minutes, 3 hours and 6 hours after coronary occlusion was 102 ± 9, 107 ± 13 and 102 ± 12 in the treated group with a hypoperfused zone less than 15% of the left ventricle and 99 ± 3, 111 ± 4 and 107 ± 3 mm Hg in the treated group with a hypoperfused zone more than 15% of the left ventricle (NS).

Discussion

This study indicates that the effectiveness of pharmacologic intervention in reducing infarct size is related to the size of the initial risk area, i.e., hypoperfused zone. Thus, more striking salvage of ischemic myocardium was observed when the hypoperfused zone was small.

Pathophysiology of the area at risk: The size of a myocardial infarction depends on the magnitude of collateral flow at the border of the hypoperfused zone as well as on myocardial oxygen consumption.

Several investigators[4,10,11] reported the presence of a flow gradient from the border zone to the center of an infarct, with a modest increase of collateral flow to the epicardial portion of the ischemic zone 24 hours after the onset of ischemia.[10–12] Because our study was limited to 6 hours of coronary occlusion, spontaneous changes in collateral flow within the ischemic zone were unlikely to occur. Striking myocardial salvage in dogs with smaller risk areas may be attributed only in part to the increase in collateral flow within the ischemic zone caused by some of the interventions used in this study, such as nifedipine[13,14] or diltiazem.[15] In contrast, other treatments, such as rutosides[6] or cytochrome C (Maroko PR, Krol R: unpublished data), did not change regional myocardial blood flow after coronary occlusion.

These findings indicate that marked myocardial salvage in dogs with a small area at risk does not require an absolute increase in collateral perfusion. The observed difference in infarct size reduction was also not related to changes in myocardial oxygen consumption, as indicated by similar heart rates and arterial pressures between the treated groups with small and large risk areas.

Determination of area at risk: Several investigators[1,4,16,17] defined the area at risk by postmortem injection of radiopaque gels or a dye solution into the occluded and nonoccluded coronary arteries. These methods, however, were limited by penetration of the dye from the normal zone into the infarcted region[4] and the need for artificial pressure required for filling of coronary arteries with a given material.[1,4,17] More im-

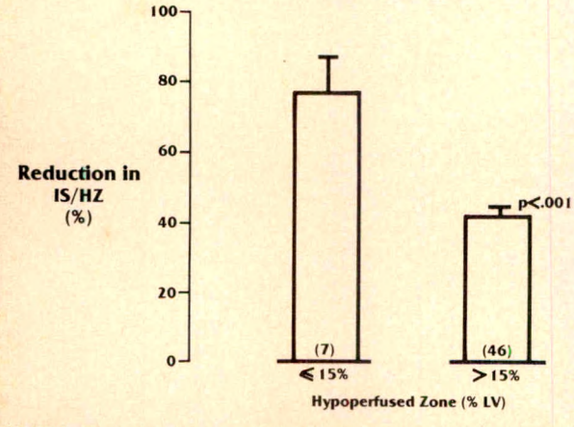

FIGURE 3. Reduction in infarct size/hypoperfused zone ratio (IS/HZ) in 2 treated groups according to the initial size of the hypoperfused zone. More striking myocardial salvage was observed in the treated group with the hypoperfused zone of less than 15% of the left ventricle (LV). Values are mean ± standard error of the mean.

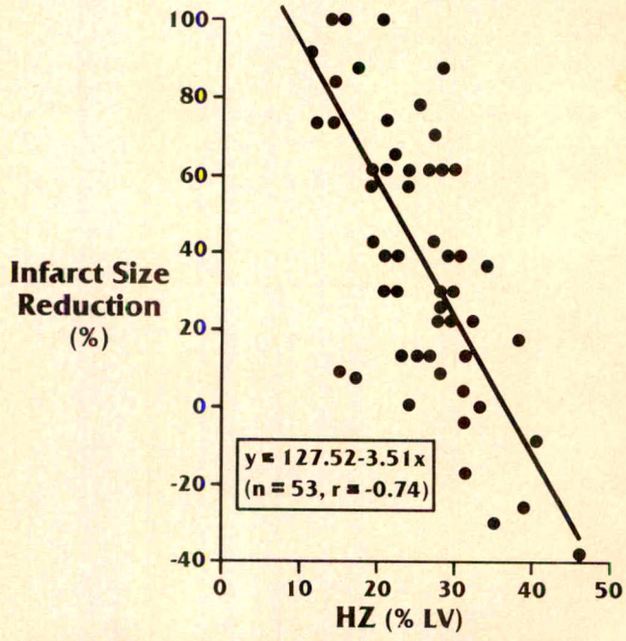

FIGURE 4. Relation between hypoperfused zone (HZ) expressed as a percent of the left ventricle (% LV) and infarct size reduction, i.e., myocardial salvage in the treated group. A close inverse correlation was found (r = −0.74), indicating that myocardial salvage is a continuous function of the initial risk area.

portant, postmortem techniques may not accurately delineate the hypoperfused areas present in vivo at the moment of coronary occlusion.

The area at risk can also be determined in vivo by contrast echocardiography[18] or injection of dye[14] or radioactive material into the left atrium[3,19] after coronary occlusion. The last technique, using postmortem autoradiography, allows for precise measurement of the hypoperfused zone present at the time of injection of the radioactive material. In our study, injection of technetium-99m-labeled albumin microspheres into the left atrium was performed after coronary occlusion before any intervention was started. Thus, this experimental technique allowed not only for in vivo determination of the hypoperfused zone, but also the potential effect of pharmacologic interventions on the measured area of hypoperfusion was avoided.[17]

Limitations of the study: The present study has several limitations. All dogs underwent occlusion of the proximal left anterior descending coronary artery; therefore, a smaller number of dogs had hypoperfused zones of less than 15% of the left ventricle. However, this emphasizes the importance of the risk area determination even with proximal coronary artery occlusions, as collateral-dependent hypoperfused zone may vary substantially. Furthermore, the investigation of interventions aimed at reducing infarct size are best studied when the initial risk area is accurately determined. The comparison of the treated groups with hypoperfused zones less than and greater than 15% of the left ventricle is arbitrary, but further analysis showed that infarct size reduction is a continuous function of the initial hypoperfused zone (Fig. 4). Therefore, the effectiveness of the treatment was inversely related to the initial areas at risk.

Clinical implications: Few data exist concerning the relation between risk area and infarct size in patients. Lee et al[20] showed a close linear correlation between the size of the vascular bed at risk and the infarcted zone in an autopsy study limited to fatal infarcts. In patients with multivessel coronary artery disease and collateral circulation supplied by a jeopardized coronary artery, acute coronary artery occlusion may lead to ischemia in the collateral-dependent zone. This phenomenon could be responsible for "ischemia at distance"[21] and is associated with a high risk of mortality.[22] This underscores the prognostic importance of the concept of area at risk. Although interpolation of our experimental findings to patients with acute myocardial infarction is difficult, preliminary data suggest that patients with a small risk area may benefit more from pharmacologic interventions aimed at salvaging ischemic myocardium. Gold et al[23] showed that intravenous propranolol administration resulted in striking reduction of ST-segment elevation in patients with acute myocardial infarction only if residual flow to the infarcted zone was preserved, i.e., the risk area was relatively small.

In conclusion, the size of the hypoperfused zone i.e., risk area, is an important determinant of the magnitude of myocardial salvage when different pharmacologic interventions are used in the setting of coronary artery occlusion in dogs. We postulate that the striking infarct size reduction in dogs with a small hypoperfused zone was related to the presence of collateral circulation, which afforded better penetration of the agents into the ischemic zone.

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Usefulness of Defibrotide in Protecting Ischemic Myocardium from Early Reperfusion Damage

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Defibrotide, a partially depolymerized polydeoxyribonucleotide obtained from mammalian lungs, was found to stimulate prostacyclin (PGI_2) production and to possess significant antithrombotic and fibrinolytic activities. The present study was designed to evaluate the actions of defibrotide on feline myocardial ischemia, produced by 3 hours of occlusion of the left anterior descending coronary artery (LAD) and followed by 2 hours of reperfusion. Intravenous administration of defibrotide (32 mg/kg/hour subsequent to a 32 mg/kg bolus injection), beginning 30 minutes after LAD occlusion, resulted in a 60% reduction in loss of CK specific activity from ischemic myocardium at 5 hours, while the nonischemic myocardium remained unaffected. Defibrotide largely antagonized the increase in ST segment during LAD occlusion and prevented the appearance of a Q wave during early reperfusion, which was found in all vehicle-treated cats. Although 2 of 8 vehicle-treated cats died from ventricular fibrillation and another had severe ventricular tachyarrhythmia, none of the defibrotide-treated cats had similar severe changes in the electrocardiogram and all 7 cats survived the 5-hour observation period. Defibrotide had no direct action on general hemodynamic functions. In a separate set of experiments, defibrotide (0.1 mg/ml) produced an 8- to 10-fold stimulation of PGI_2 release. The data suggest a remarkable protective potential of defibrotide on reperfusion damage of the ischemic myocardium, which may be associated with a PGI_2-related mechanism.

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Myocardial damage often results from acute thrombotic occlusion of a large coronary artery. Thus, surgical reopening of the occluded vessel and pharmacologic thrombolysis with streptokinase or urokinase[1] are the most direct approaches to supply the jeopardized myocardium with oxygen and other nutrients, necessary for cell survival. However, there is always an interval after the acute event before attempts to reopen the occluded vessel can be started. During this period a significant degree of tissue injury may have already developed.[2] This will eventually lead to the "reperfusion damage"[3] caused by cellular Ca^{++} overload[4] and increased free radical formation[5] after restitution of blood supply. Thus, successful thrombolysis may initially further aggravate myocardial tissue injury.[6]

Noxious stimuli to the cell surface also increase the local fatty acid release. Fatty acid peroxides can specifically inhibit prostacyclin (PGI_2) generation (i.e., formation of a tissue-protective factor) at a time when formation of other eicosanoids including thromboxanes are probably increased. PGI_2[7] and a PGI_2 mimetic[8] were found to protect the ventricular myocardium of the cat from both ischemic injury and reperfusion damage.[9] An alternative approach is to stimulate the endogenous PGI_2 production. Defibrotide is a polydeoxyribonucleotide obtained by controlled depolymerization of DNA from mammalian lungs. The molecular weight of single strands is about 20,000 daltons.* Defibrotide has significant antithrombotic-,[10] profibrinolytic-[11] and plasminogen-activating properties.[12] This profile of actions made the compound interesting as a new therapeutic approach to improve preservation of ischemic myocardium.

This study was designed to evaluate the actions of defibrotide on functional and biochemical variables of myocardial tissue damage in an in vivo model of ischemia plus reperfusion. Additionally, the influence of defibrotide on cardiac PGI_2 and thromboxane formation was investigated in the isolated guinea pig heart.

Methods

Surgical techniques: Adult cats of either sex (body weight 2.5 to 4.0 kg) were anesthetized with 30 mg/kg of pentobarbital sodium intravenously. All cats underwent tracheotomy, and positive pressure ventilation was instituted by means of a small animal respirator (Schuler). After thoracotomy, the left anterior descending artery (LAD) was prepared and occluded at time 0. This occlusion was maintained for 3 hours and then followed by 2 hours of reperfusion, initiated by removal of the ligature. All cats were killed at 5 hours.

Physiologic measurements: A catheter was placed in the right femoral vein for infusion of the substances; another was

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* British patent No. 1,367,655 (1975) and U.S. patent Nos. 3,770,720 (1973); 3,829,567 (1974); and 3,899,481 (1975).

placed in the right atrium through the right jugular vein for blood sampling. A third catheter, placed in the left femoral artery, was connected with a Statham P23Db pressure transducer to determine mean arterial blood pressure. Heart rate was determined from the systolic pressure curves by a Hellige Recomed measuring unit (Hellige). Changes in the electrical activity of the myocardium were detected by a standard lead electrocardiogram (ECG).[8]

Platelet aggregation studies: The platelet count was determined in right atrial blood by using interference phase contrast microscopy (see Ref. 8 for details).

Platelet ATP secretion: Platelet ATP secretion was measured in whole blood using a Lumi-aggregometer (Chronolog). One milliliter of right atrial blood was taken in citrate (1:10/v:v) and 1 minute later stimulated ex vivo at 37°C by the addition of 2 μg/ml of collagen (Hormon-Chemie). The samples were stirred at 1,200 rpm. ATP secretion was measured by the luminescence technique following recommendations of the producer. Synthetic ATP (Sigma) was used as the standard.

Myocardial biochemical measurements: At the end of the 5-hour experimental period, the hearts were excised and immediately placed into cold physiologic saline solution. The left ventricular wall of the heart was divided into normal and ischemic myocardium by visual inspection of the myocardial surface. Samples that weighed about 400 mg from the center of the ischemic region and of the nonischemic left ventricular tissue were excised. These tissue samples were homogenized and used for determination of CK-specific activity as previously described.[7,13] The assay kit was purchased from Boehringer.

Evaluation: LAD occlusion was performed at time 0. At 30 minutes, an intravenous bolus injection of 32 mg/kg of defibrotide (Crinos Pharmaceuticals) was performed. The substance was continuously infused in a dose of 32 mg/kg/hour for the remainder of the experiment. Cats that did not receive defibrotide were treated with physiologic saline solution (vehicle) at the same infusion rate (0.9 ml/hour). At 3 hours, the LAD occlusion was removed to allow a subsequent 2-hour reperfusion period until the end of the experiment at 5 hours. Blood samples for platelet studies were taken at 0, ½, 1, 3 and 5 hours. At the same time, platelet ATP secretion was determined ex vivo. Mean arterial blood pressure, heart rate and ECG were continuously recorded. Detailed analysis, however, was only performed at the times mentioned.

Four groups of cats were studied: cats with occluded LAD treated with vehicle (n = 9) or defibrotide (n = 7), and sham-operated cats subjected to all of the same operative procedures except closure of the LAD and treated with vehicle (n = 5) or defibrotide (n = 2). Because the 2 sham-operated, defibrotide-treated cats did not differ from the vehicle-treated controls, these data were pooled.

Prostacyclin formation by the heart: The action of defibrotide on PGI_2 biosynthesis was investigated in a separate set of experiments, using a platelet-perfused in vitro heart model.[14] Briefly, washed human platelets (4×10^8/min) were continuously infused through a Langendorff-perfused guinea pig heart. The release of PGI_2 into the coronary effluent was measured by radioimmunoassay in terms of the chemically stable degradation product 6-keto-$PGF_{1\alpha}$. The cross-reactivity of the antibody amounted to less than 0.1% with the agents used in this study: $PGF_{1\alpha}$, 15-keto-$PGF_{1\alpha}$, 15-keto-13,14-dihydro-$PGF_{1\alpha}$; 0.2% with PGD_2, 0.4% with PGE_3, 2.5% with 6,15-diketo-$PGF_{1\alpha}$ and 3% with 6,15-diketo-13,14-dihydro $PGF_{1\alpha}$. Measurements were performed before and in 10-minute intervals during platelet administration. Defibrotide (0.1 mg/ml) and urokinase (Ukidan®) (10 IU/ml) were continuously infused for 90 minutes. In some experiments indomethacin (3 μg/ml) (Merck, Sharp & Dohme) was used to block cyclooxygenase activity.

Statistical analysis: The mean ± standard error of the mean of the number of observations are used in the text. Statistical comparisons were made with the Student 2-tailed t test. A p value ≤ 0.05 was considered significant.

Results

Defibrotide effects on general hemodynamics: Initially, the mean arterial blood pressure was not different in the several groups of cats studied; it ranged from 120 to 140 mm Hg. In the cats subjected to LAD occlusion plus reperfusion and treated with vehicle, the arterial blood pressure decreased from 140 ± 4 mm Hg at time 0 to 133 ± 4 mm Hg at 5 hours. Cats treated with defibrotide had an initial blood pressure of 135 ± 5 mm Hg and 115 ± 6 mm Hg at 5 hours. These values at 5 hours were not different from each other ($p > 0.05$).

The average heart rate initially ranged from 170 to 195 beats/min in the cats subjected to LAD occlusion and was reduced by about 15% of this control level in the course of the experiment. These differences between vehicle- and defibrotide-treated cats were not significant ($p > 0.05$).

Defibrotide effects on platelet aggregate formation: Initially, the free platelet number in right atrial blood ranged from 400,000 to 550,000 platelets/μl (100%) and was uniformly decreased by 20 to 25% in all groups of cats during the operative procedures. After LAD occlusion, there was a further 20% decrease in free platelet count, which then remained unchanged in vehicle-treated cats. Even after institution of reperfusion at 3 hours, there was no restitution of the original platelet number, i.e., no resolution of platelet aggregates. There was no change in sham-operated cats nor

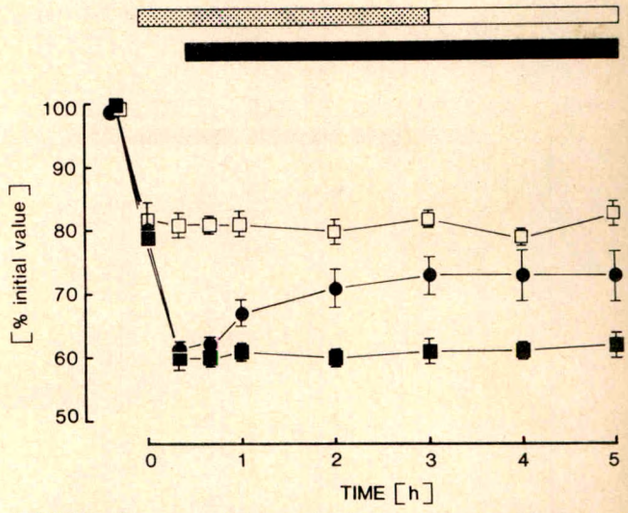

FIGURE 1. Changes in the free platelet count in cats subjected to 3 hours of occlusion of the left anterior descending coronary artery (LAD) (**stippled bar**) followed by 2 hours of reperfusion (**open bar**). The cats were treated with vehicle (**squares**) or defibrotide (32 mg/kg/hour) (**circles**) and subjected to LAD occlusion (**filled symbols**) or sham operation (**open symbols**). Each point represents the mean ± standard error of the mean of 7 to 8 experiments. In comparison with cats with occluded LAD treated with vehicle, there was a significant elevation of the free platelet count in defibrotide-treated cats at 2 to 5 hours (h).

TABLE I ATP Secretion in Whole Blood Ex Vivo of Cats Subjected to Left Anterior Descending Coronary Artery Occlusion (LAD) + Reperfusion and Treated with Vehicle or Defibrotide

Group	No.	ATP Release (% of Control = Time 0)				
Time after LAD occlusion (hour)		0	30 minutes	1½	3	5
Vehicle	7	100%	88 ± 15	67 ± 7	75 ± 24	80 ± 23
Defibrotide	6	100%	86 ± 14	36 ± 10	29 ± 6	23 ± 5

Values are mean ± standard error of the number of observations. Compared with the group treated with vehicle, the ATP secretion in the defibrotide-treated group was significantly reduced at 1.5, 3 and 5 hours ($p < 0.05$).

any direct action of defibrotide on platelet number in these cats (not given). However, cats with LAD ligation treated with defibrotide had a significant increase in the free circulating platelet count ($p < 0.05$ at 2 to 5 hours compared with values after vehicle treatment) (Fig. 1).

Defibrotide effects on platelet ATP secretion: Cats with occluded LAD treated with vehicle showed slightly reduced ATP secretion during the course of the experiment ($p > 0.05$). This ATP release was highly variable and not different from that of sham-operated controls at any time of the experiment. However, cats subjected to LAD occlusion and treated with defibrotide had a considerable reduction in ATP release which was significant at 1.5, 3 and 5 hours (Table I).

Defibrotide effects on ST-segment elevation: LAD occlusion was associated with rapidly developing ST-segment elevation, which was greatest at 3 hours (Fig. 2). Removal of the occlusion at this time resulted in a rapid decrease, although a significant ST-segment elevation greater than that in sham-operated controls was still observed ($p < 0.05$ from 20 minutes to 5 hours). The cats with LAD occlusion treated with defibrotide had a significant increase in ST segment at 20 minutes, i.e., before starting drug administration. After starting infusion, there was no further increase in the ST segment; in fact, there was a reduction, almost similar to the values in sham-operated, vehicle-treated cats. The differences between the cats with LAD occlusion treated with vehicle and the defibrotide group were significant at 1 to 3 hours ($p < 0.05$). At 4 and 5 hours, during reperfusion, there was no significant difference between cats with LAD occlusion that received defibrotide and sham-operated controls.

Defibrotide effects on R-wave loss: Within a few minutes of reperfusion, there was a decrease in R-wave amplitude and appearance of a Q wave, suggestive of ventricular necrosis. Two of 8 vehicle-treated cats died from ventricular fibrillation within 20 minutes of reperfusion; another had ventricular tachycardia and frequent ventricular extrasystoles that did not lead to lethal fibrillation. No such changes were observed in defibrotide-treated cats.

Defibrotide effects on myocardial CK activity: Ischemic myocardium subjected to reperfusion exhibited more than 80% loss of CK specific activity. No such changes were observed in the nonischemic area of the left ventricle of the same hearts. As summarized in Figure 3, the CK-specific activity in the ischemic area of defibrotide-treated cats ($p < 0.01$) was as much as 3-fold higher than in vehicle-treated cats, although still significantly lower than in the nonischemic area of the

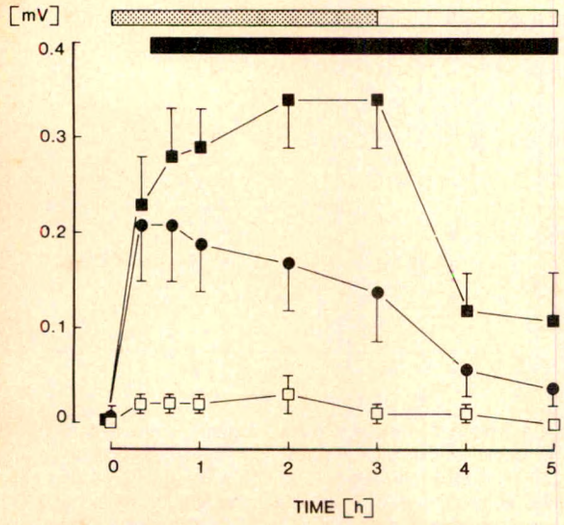

FIGURE 2. ST-segment elevation in cats subjected to 3 hours of occlusion of the left anterior descending coronary artery (LAD) followed by 2 hours of reperfusion. In comparison with cats with occluded LAD treated with vehicle (**filled squares**), there was a significant reduction of ST-segment elevation in defibrotide-treated cats with LAD occlusion (**filled circles**) at 1 to 5 hours (h).

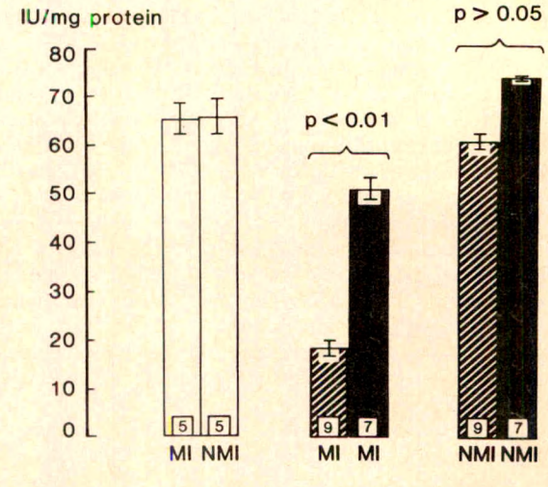

FIGURE 3. Creatine kinase specific activity in ischemic (MI) and nonischemic (NMI) areas of left ventricular myocardium of cats subjected to 3 hours of occlusion of the left anterior descending artery followed by 2 hours of reperfusion. The cats were treated with vehicle (**hatched columns**) or defibrotide (**black columns**). **Open columns** depict sham-operated, vehicle-treated controls. Numbers indicate the number of cats studied.

same hearts ($p < 0.05$). This result might not be explained by any specific action of defibrotide on the enzyme itself as seen in 2 additional, sham-operated cats treated with the agent. The CK-specific activity was 78 and 80 IU/mg of protein, respectively, and not different from the vehicle-treated, sham-operated controls.

Defibrotide effects on prostacyclin biosynthesis: Infusion of platelets through an isolated heart was not associated with any changes in basal PGI_2 release. However, if defibrotide was added to the system, the PGI_2 release was considerably enhanced. This effect was blocked by indomethacin pretreatment and was not seen when urokinase instead of defibrotide was used (Fig. 4). Details of the complex platelet studies require particular comments and will be reported separately. For the present study, the capacity of the agent to stimulate cardiovascular PGI_2 release should be demonstrated. Two additional findings are particularly noteworthy: defibrotide did not stimulate PGI_2 in absence of platelets and also did not specifically alter thromboxane release. Thus, defibrotide appears to be a selective stimulator for PGI_2.

Discussion

Myocardial protection by defibrotide: Earlier studies in the ischemia + reperfusion model of the cat have shown that CK loss from the ischemic area of left ventricular myocardium is 2- to 3-fold greater after 3 hours of LAD occlusion + 2 hours of reperfusion than after 5 hours of permanent LAD ligation.[9] This enzyme loss was found to be inversely proportional to the extent and severity of myocardial cell damage.[15] Defibrotide inhibited the CK loss from ischemic myocardium. This is highly suggestive of improved preservation of tissue integrity by the compound. This finding is corroborated by the inhibition of Q-wave development in the ECG, a widely accepted sign for irreversible cell injury as well as the prevention of fatal arrhythmias.

Recent investigations by Niada et al[16] demonstrated protective actions of defibrotide on ischemic cat myocardium subjected to 5 hours of permanent LAD occlusion. In these experiments, administration of defibrotide was begun 3½ hours before LAD occlusion; in our experiments, infusion was begun at only 30 minutes after LAD occlusion, i.e., at a time when significant alterations in myocardial function were already detectable, such as a considerable increase in the ST segment. Thus, our findings not only demonstrate the efficacy of defibrotide in preventing reperfusion damage but also show that the compound may be valuable for a real therapeutic approach (i.e., successful use after a period of ischemia had occurred).

Defibrotide actions on hemostasis: Reperfusion allows exaggerated platelet entry (10- to 30-fold) into the jeopardized region of left ventricular myocardium.[17,18] This may explain the sustained depression of free platelet count during reperfusion. Defibrotide did redissolve preformed platelet aggregates in vivo and inhibited platelet ATP secretion, although the compound does not possess antiplatelet properties in vitro. Stimulation of vascular PGI_2 by defibrotide could explain these apparent discrepancies, because similar antiplatelet effects have been found in this model with administration of PGI_2 mimetics.[9] Certainly, defibrotide may additionally improve the blood supply to the border zone of the developing infarct by its fibrinolytic activity.[10–12]

Prostacyclin stimulation with defibrotide: Myocardial ischemia is associated with a large increase in tissue free fatty acids[21] and enhanced formation of thromboxane A_2.[20] Reperfusion will increase free fatty acid washout and may initiate the formation of free radicals as toxic by products of an abnormal oxidative metabolism.[5] Lipid peroxidation products will inhibit PGI_2 biosynthesis. Thus, reduced formation of PGI_2 could contribute to the reperfusion injury of ischemic myocardium, whereas supply with PGI_2 will afford protection.[21] However, drug-induced stimulation of PGI_2 in vivo is difficult to assess because of its instability and rapid enzymatic metabolism.[22] Also, the use of cyclooxygenase-blocking agents to demask any enhanced PGI_2 formation in vivo may be inappropriate because of known but unidentified reasons for their failure[23] or effectiveness[24] in beneficially influencing the tissue damage in myocardial ischemia in the cat. We therefore, have decided to measure the influence of defibrotide on PGI_2 formation in a separate experimental design that allows determination of this compound in terms of a stable degradation product in the absence of significant enzymatic transformations.[14] These studies have shown long-lasting PGI_2 stimulation by defibrotide in the presence of platelets exceeding the basal PGI_2 release 8- to 10-fold. We were not able to demonstrate a similar effect with urokinase at an equieffective fibrinolytic concentration. Thus, although fibrinolytic- and plasminogen-activating actions of defibrotide are similar to that seen after streptokinase or urokinase,[16] the former additionally stimulates coronary vascular PGI_2, whereas urokinase does not.

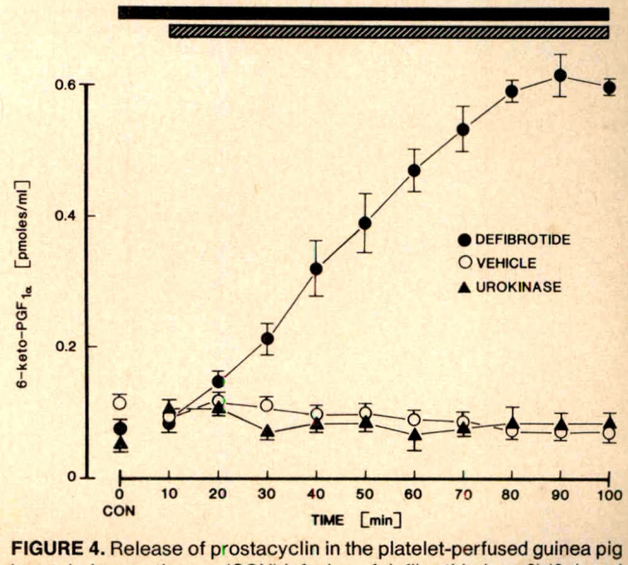

FIGURE 4. Release of prostacyclin in the platelet-perfused guinea pig heart during continuous (CON) infusion of defibrotide (n = 6) (0.1 mg/ml) but not by vehicle (n = 8) treatment. Urokinase (10 IU/ml) (n = 3) failed to stimulate prostacyclin.

In conclusion, defibrotide exerts an impressive protection of ischemic myocardial injury after reperfusion. All of the responses are close to those obtained with PGI_2 in similar experimental set-ups and may have this endogenous product as a common denominator. In agreement with this, a selective stimulation of coronary vascular PGI_2 by defibrotide has been demonstrated.

Acknowledgment: We are grateful to Crinos Pharmaceuticals (Villa Guardia, Como, Italy) for generously supplying us with defibrotide and urokinase, to Werner Rücker, PhD, and Bernhard A. Peskar, MD, for preparation of the 6-keto-$PGF_{1\alpha}$ antibody and to Edward F. Smith III, PhD, for stimulating comments.

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The Healing Process in Normal Canine Arteries and in Atherosclerotic Monkey Arteries After Transluminal Laser Irradiation

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To evaluate the healing response of both normal and atherosclerotic arteries to laser radiation, 7 mongrel dogs and 4 hypercholesterolemic atherosclerotic monkeys underwent catheterization with a right Judkins catheter-optical fiber system designed to maximize arterial wall injury. Argon laser radiation was then delivered to the abdominal aorta and iliofemoral arteries. In the 11 animals, a total of 917 sites were irradiated in 33 arteries. Angiography did not reveal dissection or aneurysm formation; occlusive thrombosis was found in 2 arteries. Perforation of the arterial wall was a frequent complication. In animals killed between 1 hour and 4 days, light and electron microscopy of lased sites showed craters filled with a coagulum of blood and cellular debris with only a few adherent platelets. Healing occurred with a minimal inflammatory response and involved both fibroblasts and smooth muscle cells. Reendothelialization was seen in all animals killed between 7 and 14 days after lasing and was complete by 30 to 60 days. Within this period, no accelerated atherosclerosis was seen at lased sites in the hypercholesterolemic monkeys. It is concluded that transluminal lasing of normal arteries in dogs and in atherosclerotic arteries of monkeys is followed by healing and reendothelialization within a few weeks.

(Am J Cardiol 1985;56:983–988)

Lasers can recanalize occluded arteries.[1–5] During laser recanalization, however, areas of both normal and atherosclerotic arterial wall adjacent to the occluded segment may be inadvertently exposed to radiation. Therefore, before clinical application of this technique for recanalization, the irradiated arterial wall must heal without occlusive thrombus or aneurysm formation.[6] Also, one must know whether lasing in the presence of hypercholesterolemia accelerates atherosclerosis, similar to the response to other types of vascular trauma.[7–11]

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This study was designed to investigate the immediate and short-term healing responses after laser irradiation of the arterial wall in normal and hypercholesterolemic atherosclerotic animals. With this technique, maximal laser trauma to the arterial wall is expected to occur. This type of trauma may occur during the course of laser recanalization. Energies known to vaporize atherosclerotic plaques were delivered through the optical fiber using a transluminal approach.[1,5] The transluminal approach was used to avoid an arteriotomy at the lased site, which itself could influence the results.[12,13]

Methods

Delivery of laser radiation: A continuous-wave argon laser (model 552, Laser Ionics) or Endocoagulator ML8, with energy peaks at wavelengths of 488 and 514 nm was used. Radiation was delivered through a 150-cm-long, 300-μm core silica optical fiber polished smooth at both ends. One end was aligned with the focused beam as it exited the laser, while the free end was used for lasing. Because of power attenuation along the fiber, radiation power was measured at the fiber tip with an external power meter. Because the fiber is not radiopaque, a metal marker was fixed at the tip allowing fluoroscopic visualization.

Protocol: *Mongrel dogs:* Eight mongrel dogs (19 to 22 kg) were anesthetized with an equal mixture of pentobarbital and fentanyl, intubated and allowed to ventilate spontaneously on a mixture of room air and halothane. A single dose of

TABLE I Summary of Angiographic and Postmortem Findings in Dogs and Monkeys

	Lased Sites (n)			Before Lasing Angiography			After Lasing Angiography			Time to	Before Death Angiography			Postmortem Examination		
Dog	Ao	LIF	RIF	Ao	LIF	RIF	Ao	LIF	RIF	Death	Ao	LIF	RIF	Ao	LIF	RIF
							Dogs									
1	0	0	0	N	N	N	N	N	N	1 Hour	N	N	N	N	N	N
2	26	21	21	N	N	N	N	N	P	1 Hour	N	N	N	PH	PH	PH
3	28	26	20	N	N	N	N	N	N	2 Days	N	N	N	PH	PH	PH
4	18	27	27	N	N	N	N	N	N	4 Days	N	N	N	PH	PH	PH
5	29	29	27	N	N	N	P	N	N	7 Days	N	N	N	PH	PH	PH
6	25	28	26	N	N	N	N	N	N	14 Days	N	N	N	PH	PH	PH
7	30	25	36	N	N	N	N	N	P	30 Days	N	N	N	N	N	N
8	30	26	19	N	N	N	N	N	N	60 Days	N	N	N	N	N	N
							Monkeys									
1	39	18	18	N	N	N	N	N	P	7 Days	N	N	N	PH	N	PH, T
2	42	34	17	N	N	P	N	N	N	14 Days	N	N	T*	N	N	T*
3	34	31	28	N	N	N	N	N	P	30 Days	N	N	N	N	N	N
4	43	32	37	N	N	N	P	N	N	60 Days	N	T	N	N	T	N

* Thrombosis occurred in the segment perforated during fiber manipulation.
Ao = Aorta; LIF = left iliofemoral artery; N = normal; P = arterial perforation; PH = perivascular hematoma; RIF = right iliofemoral artery; T = thrombosis.

heparin (1,000 IU) was administered intravenously before catheterization. No antiplatelet agents were used. A No. 8Fr right Judkins catheter (Cordis Corp.) was introduced through a right carotid cutdown and advanced to the abdominal aorta. A hemostasis valve and special seal port allowed for simultaneous contrast injection and placement of the optical fiber. Cineangiograms of the distal aorta and both iliofemoral arteries were recorded. The radiopaque tip of the fiber was advanced 1 to 2 mm beyond the catheter. Because of the shape of the catheter, the fiber tip exited at an acute angle and abutted on the arterial wall. This ensured maximal delivery of energy to the arterial wall. In 7 dogs, multiple 1-second lasings were done starting from the distal end of the iliofemoral arteries. After each lasing, the catheter and the optical fiber were withdrawn 0.5 to 1 cm and lasing was repeated. A power of 1.5 W was used in the left iliofemoral artery, 2 W in the right iliofemoral artery and 2.5 W in the distal aorta. From these parameters energy flux was calculated to be 2,100 J/cm^2, 2,800 J/cm^2 and 3,500 J/cm^2, respectively. These parameters were selected because they were the minimum required to vaporize atherosclerotic plaque by direct fiber tissue contact.[1] One dog in which no lasing was performed served as a control for catheter and fiber trauma. Repeat cineangiography was obtained in each dog within 30 minutes of the last lasing. The control dog and 1 lased dog underwent repeat angiography and were killed after 1 hour. The other 6 dogs were allowed to recover, underwent repeat angiography and were killed at 2, 4, 7, 14, 30 and 60 days.

Atherosclerotic monkeys: Four male 3-year-old rhesus monkeys (*Macaca mulatta*) (6 to 8 kg) were fed an atherogenic diet since weaning (Bio Serve 1206). Anesthesia, catheterization and angiography were performed as previously described, except that a No. 5Fr thin-walled right Judkins catheter (Cordis Corp.) was used. All monkeys were allowed to recover. Angiography was repeated and the monkeys were killed at 7, 14, 40 and 60 days. Monkeys continued to receive the atherogenic diet after lasing until they were killed. The average serum cholesterol level before death was 392 mg/dl.

Gross inspection and histology: Immediately after death, the distal aorta and both iliofemoral arteries were removed, opened longitudinally and inspected. Tissues were fixed either in 10% neutral buffered formalin for light microscopy or in 2.5% gluteraldehyde in 0.2 *M* cacodylate buffer for scanning and transmission electron microscopy (SEM and TEM). Formalin-fixed tissues were dehydrated promptly through graded alcohols and embedded in paraffin blocks. From each artery, samples from lased areas were cut serially at a thickness of 5 μm and stained with hematoxylin-eosin or Verhoeff's elastic stain. Gluteraldehyde-fixed, 5-mm-long arterial segments containing a lased area were subjected to critical point drying in liquid CO_2, mounted on stubs and gold coated in a sputter coater for SEM. The intimal surface was examined with a JEOL 35 C electron microscope. The remaining samples were used for TEM. Lased areas were cut into 2-mm pieces, embedded in Spurr resin and thin-sectioned with a diamond knife. Sections were stained with uranyl acetate and lead citrate and viewed in a Phillips 300 electron microscope.

The incidence of angiographic evidence for arterial perforation in the left and right iliofemoral arteries was compared using Fisher's exact test. A p value <0.05 was considered significant.

Results

Lasing (Table I): *Mongrel dogs:* A total of 544 areas were irradiated in 21 arteries: left iliofemoral artery, 182; right iliofemoral artery, 176; and aorta, 186. No dog died after lasing.

Atherosclerotic monkeys: A total of 373 sites were irradiated in 12 arteries: left iliofemoral artery, 115; right iliofemoral artery, 100; and aorta, 158. No monkey died after lasing.

Angiographic findings (Table I): *Mongrel dogs:* Immediately after lasing, angiography showed perivascular contrast extravasation suggestive of arterial perforation in 3 of 7 dogs, once in the aorta and twice in the right iliofemoral artery. Thirty minutes later and before death no contrast extravasation was seen. Although no perforations were seen in left iliofemoral arteries, the incidence of perforation using 1.5 and 2 W in the left (0 of 7) and right (2 of 7) iliofemoral arteries, respectively, was not significantly different. Angiography never showed arterial spasm, dissection, aneurysmal dilatation or occlusion. In the control dog, no effect of fiber-catheter manipulation was seen.

Atherosclerotic monkeys: In contrast to dogs, catheter-induced spasm of the iliofemoral arteries was a frequent occurrence in monkeys before and after lasing. In monkey 2, fiber-catheter manipulation in the right iliofemoral artery caused severe spasm, resulting in

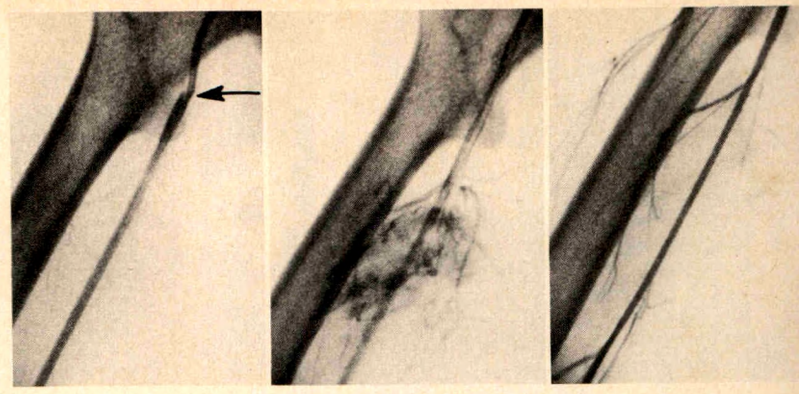

FIGURE 1. Left, angiogram of the right iliofemoral artery in a monkey before laser exposure. A right Judkins catheter was used to lase the arterial wall at an acute angle. Metal marker at fiber tip is pointed to the arterial wall (**arrow**). **Middle,** angiogram of the same artery immediately after lasing (2 W for 1 second). Extravasation of contrast material is seen. **Right,** angiogram 30 minutes after lasing showing patency of the vascular lumen with no further extravasation of contrast.The vessel walls are smooth.

perforation before lasing. All 4 monkeys underwent lasing, and angiography performed immediately after lasing showed perforation in 3 of 12 arteries (1 aorta and 2 right iliofemoral arteries). No angiographic evidence of perforation was seen on repeat angiograms recorded after 30 minutes (Fig. 1). Comparison of perforations while lasing with 1.5 and 2 W in the left (0 of 4) and right (2 of 4) iliofemoral arteries, respectively, was not significantly different. Angiography immediately after lasing never showed arterial dissection, aneurysmal dilatation or occlusion.

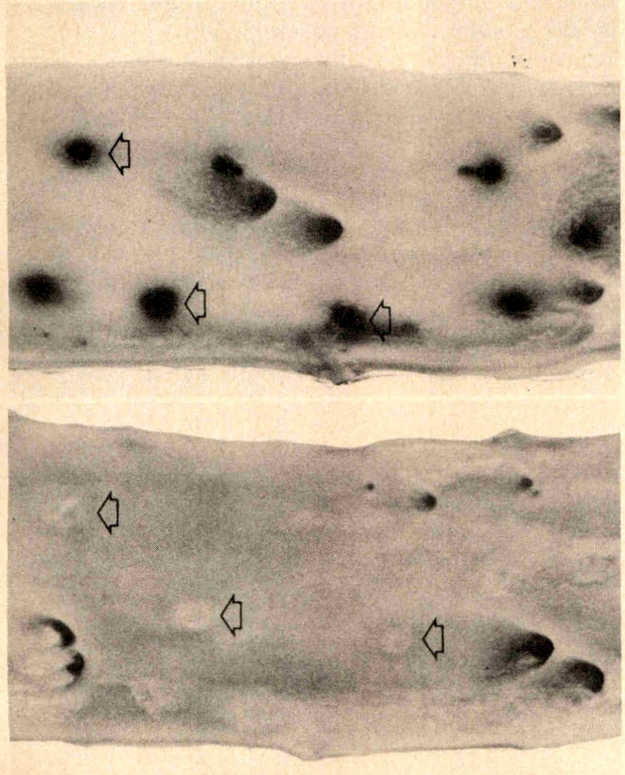

FIGURE 2. Top, gross appearance of a distal abdominal aorta from a dog at 1 week after lasing (2.5 W for 1 second). Numerous craters are present (**arrows**). There is no thrombus present. **Bottom,** gross appearance of a distal abdominal aorta from a dog 1 month after lasing (2.5 W for 1 second). The number of identifiable craters (**arrows**) is less than at 1 week. Those that are seen have a smooth, flat, white surface.

Angiography before 2 monkeys were killed at 14 and 60 days after lasing showed occlusive thrombus in 2 arteries at previously lased sites. In monkey 2, thrombosis was present in the right iliofemoral artery at the site of fiber-catheter perforation, which occurred before lasing. In monkey 4 thrombus occluded the distal end of the left femoral artery.

Gross inspection (Table I): *Mongrel dogs:* In lased dogs killed within 2 weeks, hematomas were present around both the aorta and iliofemoral arteries. In all lased dogs, raised, 1- to 2-mm reddish spots were present on the adventitial aspect of the arteries and corresponded to small craters on the intimal surface. The number of identifiable craters decreased and their depth diminished as the intervals between lasing and death increased (Fig. 2 and 3). The surface of older lesions were flat and had a glistening whitish appearance. These spots were not seen in the control dog.

Atherosclerotic monkeys: Perivascular hematomas surrounded the aorta and right iliofemoral artery in the monkey killed 7 days after lasing, but none were seen in those killed later. In all monkeys 1- to 2-mm reddish spots were present on the adventitial aspect of the arteries also corresponding with small intimal craters. Atherosclerosis was evenly distributed over the intimal surface. Similar to the dog arteries, fewer arterial craters could be identified as the interval after laser exposure increased (Fig. 3). Older lesions were flat and whitish in appearance. In monkeys 2 and 4, thrombus was seen in the 2 arteries that were angiographically occluded.

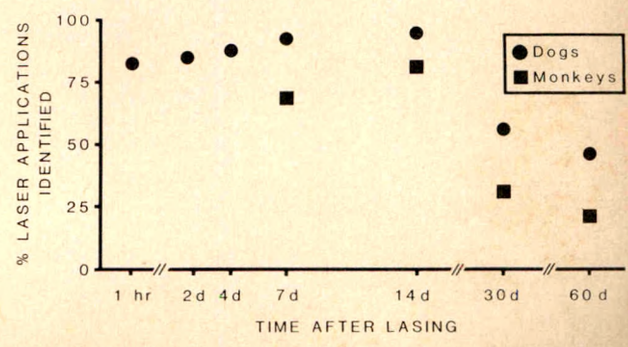

FIGURE 3. Percentage of arterial lased site identifiable by gross inspection of the intimal surface at different intervals after lasing in both dogs and monkeys. At 1 and 2 months, fewer craters are seen than at earlier periods.

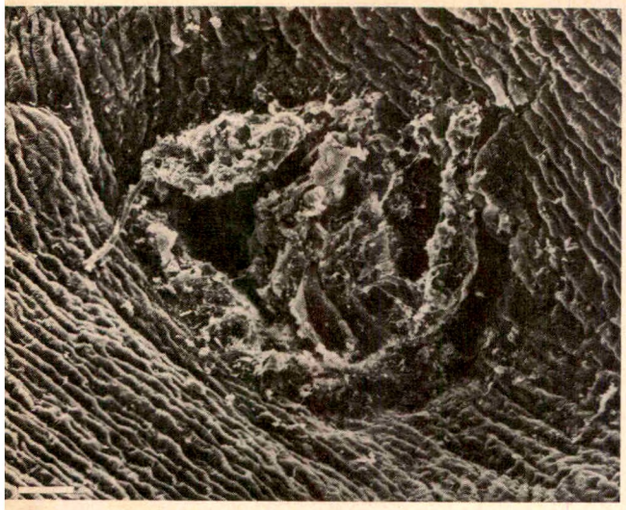

FIGURE 4. Scanning electron micrograph of the right iliofemoral artery from a dog killed 1 hour after lasing (2 W for 1 second). The crater site has sharply demarcated edges and is filled with coagulum of blood and cellular debris. Few platelets are seen. Magnification ×90, reduced by 30%. Bar = 100 μm.

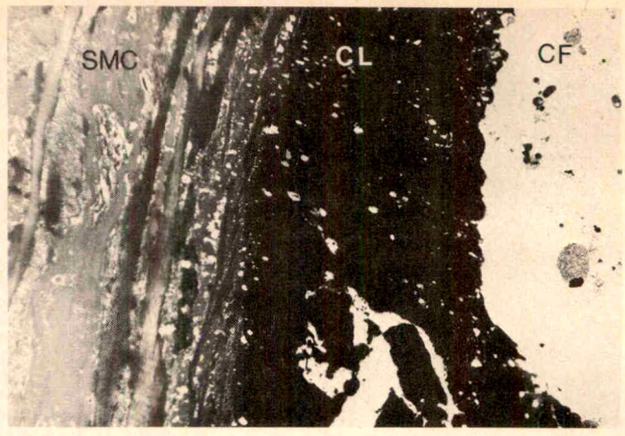

FIGURE 5. Transmission electron micrograph from the same artery as in Figure 4 showing the arterial surface 1 hour after lasing (2 W for 1 second). The surface is covered by a smooth carbonized layer (CL) seen here at the bottom of the crater overlying injured smooth muscle cells (SMC). Cellular fragments (CF) are seen loosely adherent to the lumen side of the arterial surface. Magnification ×6,600, reduced by 45%.

In monkey 1, a small thrombus was found in the distal right femoral artery at the site of lasing. This was not apparent on angiography.

Histology: *Mongrel dogs:* One hour after lasing, low-magnification SEM of the intimal surface revealed the laser impact area as a crater covered with a layer of coagulated elements with only a few adherent platelets (Fig. 4). Around the crater were occasional crenated red blood cells. Light microscopy showed that perforation of the arterial wall was sealed by thrombus. All craters were filled with a coagulum of blood and cellular debris that did not extend beyond the vascular lumen. On TEM, the coagulated edges of the crater were smooth and covered by a carbonized layer (Fig. 5). The material inside the crater was too denatured to be identified. In dogs killed at 2 and 4 days after lasing, TEM showed early healing. Healing was remarkable in that it evoked no polymorphonuclear leukocyte and only a weak mononuclear phagocyte response. By 7 days, the healing process was well under way with a low-grade cellular infiltrate consisting of smooth muscle cells and undifferentiated mesenchymal cells, probably fibroblasts. These cells were identified by TEM as cells containing prominent rough endoplasmic reticulum and absent cytoplasmic filaments with peripheral condensations. Reendothelialization was apparent at 7 and 14 days with elongated and proliferating endothelial cells partially covering the edges and surface of the craters. There was variability in the extent of reendothelialization among different craters in the same dog. Most craters were completely reendothelialized by 30 days (Fig. 6), and after 60 days all lased areas were healed.

Atherosclerotic monkeys: The arterial wall was characterized by a concentric intimal thickening mainly due to the presence of foam cells. At 7 and 14 days after lasing, the morphologic characteristic of the craters was similar to that observed in dogs. In monkeys, the mor-

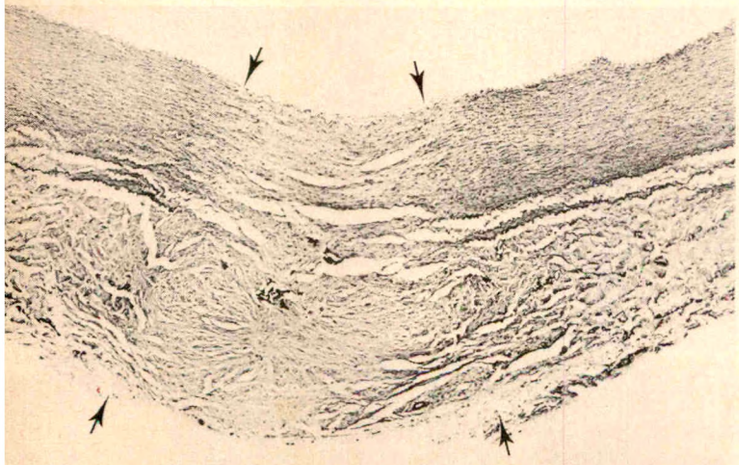

FIGURE 6. Light micrograph of a lased right iliofemoral artery from a dog killed 30 days after lasing (2 W for 1 second). **Arrows** point to lased regions. At the site of laser injury, intimal reendothelialization is complete; the media is hypocellular and the adventia appears thickened. Hematoxylin-eosin ×25, reduced by 35%.

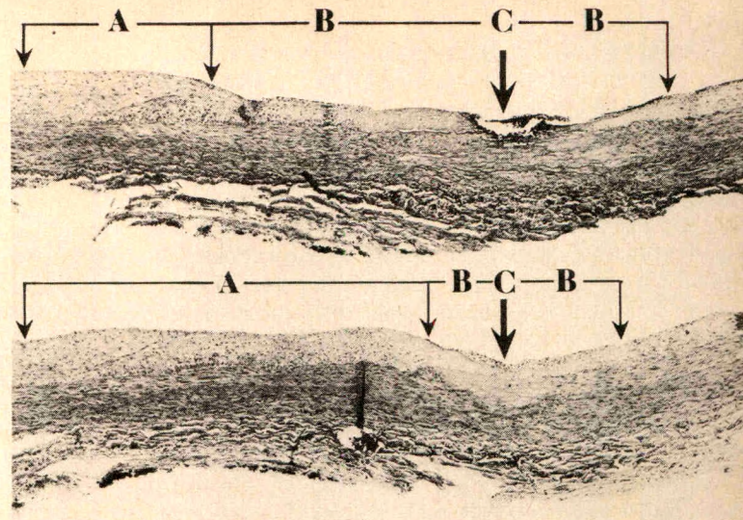

FIGURE 7. Light micrographs of hypercholesterolemic monkey aortas killed at 7 days (**top**) and 30 days (**bottom**) after lasing (2.5 W for 1 second). Zone A is the surrounding nonlased plaque; zone B is the plaque bordering the crater; zone C is the crater made by lasing. **Top,** the crater at 7 days is clearly visible with charred edges and a lumen filled with a coagulum of cellular debris. The bordering zone B is characterized by thinning of the intima, whereas the surrounding zone A shows the intimal thickening typical of this atherosclerotic model. Hematoxylin-eosin ×25, reduced by 39%. **Bottom,** the crater at 1 month is reendothelialized and hypocellular. The reformed arterial intima at the crater site as well as at the adjacent zone B is thinner than that in zone A. Hematoxylin-eosin ×25, reduced by 39%.

phologic configuration of the area adjacent to the crater was of particular interest. In these hypercholesterolemic monkeys, the intimal thickening of the atherosclerotic plaque was thinned adjacent to the crater (Fig. 7). This thinning persisted for at least 60 days and was a result of a decreased number of intimal cells. For at least 60 days, lased areas showed only minimal or no reappearance of foam cells or cholesterol deposits. At 30 and 60 days after lasing, the craters showed reendothelialization (Fig. 8).

Discussion

Laser irradiation of both muscular and elastic arteries in normal and atherosclerotic animals lead to the formation of craters that heal in 30 to 60 days. The healing process was remarkable for the following reasons: (1) Few platelets were seen near or at the lased site. (2) Injury induced by lasing did not evoke a strong inflammatory reaction. (3) Healing involved reendothelialization and participation of both smooth muscle cells and other mesenchymal cells, probably fibroblasts. The absence of platelet adhesion is especially encouraging and may explain the low incidence of occlusive thrombosis after lasing. However, the coagulated debris that filled the crater together with the formation of an extravascular hematoma appeared adequate to prevent serious leakage from the arterial lumen. The paucity of inflammatory cells involved in the healing process indicates an unusual response to injury that either evokes little chemotactic activity or inhibits inflammatory cell adherence and migration.[14] Although macrophages were not particularly prominent, their numbers appeared sufficient for debridement and possibly for promoting smooth muscle cell and fibroblast participation in repair through growth factor production.[15] Because fibroblasts are not normally a component of adult intima or media, it is presumed that they migrated into the crater from the adventia. Reendothelialization was observed to occur at various rates, but was usually completed by 30 days.

Laser radiation of atherosclerotic arteries in hypercholesterolemic monkeys did not accelerate atherosclerosis over the period studied. In these monkeys, the intima at lased sites and at the bordering areas actually appeared thinner than the surrounding nonlased intima, suggesting a persistent effect. This response to injury contrasts with reactions to other types of arterial injury such as balloon endothelial stripping, which leads to an acceleration of atherosclerosis.[7–11]

These results are encouraging and demonstrate the feasibility of lasing by the transluminal approach in the presence of blood. Extrapolation of these findings in animals to the clinical setting can be made only with caution. The pathology of human atherosclerosis is different from that in the experimental animal.[16] However, the fact that the healing process was similar in muscular and elastic arteries of normal dogs and atherosclerotic monkeys suggests that responses of

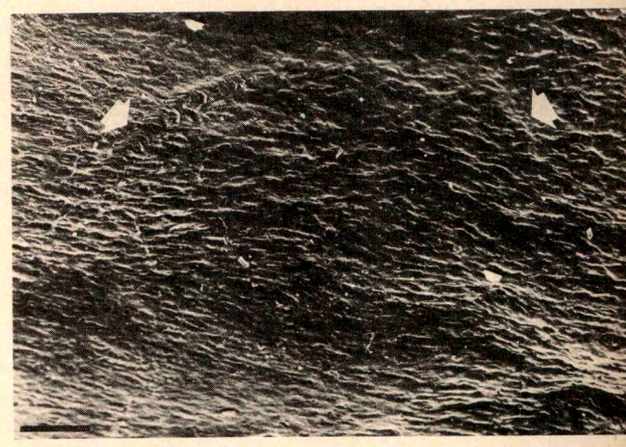

FIGURE 8. Scanning electron micrograph of the left iliofemoral artery from a monkey killed 60 days after lasing (1.5 W for 1 second). The lased site is reendothelialized and appears as a shallow depression (**arrows**) on the intimal surface of the artery. Magnification ×80, reduced by 49%. Bar = 100 μm.

different arterial walls to laser injury may be similar in other species.

Despite maximal wall damage, no dissection, occlusive thrombosis or aneurysm formation was seen in any of the normal lased dog arteries. In a previous study we found a high incidence of thrombosis after lasing, but these studies used surgically exposed arteries, and lasing was done in air adjacent to the arteriotomy.[12] A transluminal catheter approach to lasing avoids local surgical trauma which can contribute to thrombosis. Occlusive thrombosis was an infrequent event and was present in only 2 small branches of the femoral artery. Spasm or fiber-catheter trauma could have contributed to thrombus formation. In atherosclerotic pigs, the healing process of aortas irradiated with a CO_2 laser adjacent to an arteriotomy was similar to that observed in dogs and atherosclerotic monkeys.[13] That study, however, showed considerable platelet deposition, which may have been related to either the CO_2 laser, lasing in air in the absence of saline solution or blood, or the adjacent arteriotomy.

Aneurysm formation was not observed in our experiments; however, Lee et al[6] reported this complication in rabbits. In that study aneurysm formation might have been attributed to a larger and stiffer 400-μm core silica optical fiber and to rabbits having thinner arterial walls than dogs or monkeys.

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Validation of Instantaneous Pressure Gradients Measured by Continuous-Wave Doppler in Experimentally Induced Aortic Stenosis

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The relation between catheter-measured and Doppler-derived aortic pressure gradients was examined in 8 open-chest dogs. A snare was placed around the proximal ascending aorta and adjusted to provide a wide range of gradient to left ventricular (LV) outflow. A continuous-wave Doppler transducer was placed above the level of the obstruction and angled to optimize the audio and spectral signals. Pressure tip transducer catheters recorded LV and ascending aortic pressures simultaneously with the Doppler signal. In 120 randomly selected sinus beats, Doppler-derived maximal gradient correlated well with maximal instantaneous catheter gradient from 4 to 179 mm Hg ($r = 0.99$). Mean gradients also were closely related ($r = 0.98$). For gradients above 100 mm Hg, the correlation remained good ($r = 0.98$), but for gradients below 50 mm Hg, the correlation was not as precise ($r = 0.81$). All 120 cycles were digitized at 10-ms intervals to examine the correspondence between the Doppler and catheter data throughout systole. For the 2,742 pairs of points so obtained, the correlation was excellent ($r = 0.95$). The close relation between Doppler-derived pressure gradient and that measured simultaneously by catheterization provides further validation of the use of continuous-wave Doppler in the assessment of aortic stenosis, not only at maximal gradient, but throughout the period of LV ejection.

(Am J Cardiol 1985;56:989–993)

Doppler echocardiography has an important role in the noninvasive assessment of valvular heart disease. Continuous-wave Doppler has been used to measure the increased blood velocity across the aortic valve in patients with aortic stenosis (AS).[1–4] The peak aortic flow velocity is used to derive the pressure gradient across the aortic valve by means of a simplified version of the Bernoulli equation.[2] Although initial studies reported a good correlation between aortic valve gradient at catheterization and that estimated by Doppler, uncertainties remain concerning the validity of this simplification.

This study was undertaken to confirm, in a controlled experimental environment, the overall correlation of Doppler and catheterization gradients (maximum, mean and peak-to-peak) and also to investigate the instantaneous relation between aortic flow velocity and pressure gradient throughout the cardiac cycle.

Methods

Eight mongrel dogs, mean weight 19 kg (range 17 to 22.5), were anesthetized with intramuscular Innovar® (0.25 ml/kg), followed by intravenous sodium pentobarbital (30 mg/kg). The dogs were intubated and ventilated with a standard volume respirator. The heart and ascending aorta were exposed through a right thoracotomy and dissected free of adventitial fat up to the level of the arch. A Millar pressure tip transducer catheter (No. 7Fr) was inserted into the left ventricle by apical puncture. This catheter included a port that allowed injection of indocyanine green dye for cardiac output determinations. A second Millar (7Fr) catheter was introduced into the ascending aorta by carotid artery cutdown. This catheter could record an intraaortic phonocardiogram. The left femoral artery was cannulated for withdrawal of arterial blood during cardiac output determinations. A snare made of 2 mm of polyethylene tubing containing a short length of umbilical tape was placed around the proximal ascending aorta. This provided controlled, adjustable levels of obstruction to left ventricular (LV) outflow (Fig. 1).

Continuous-wave Doppler techniques: Doppler information was obtained by using a nonimaging transducer incorporated into an Irex 3-B system. The transducer was placed in a surgical glove containing ultrasonic gel and was hand-held on the ascending aorta close to the arch. Care was taken to ensure that the transducer was positioned with light pressure and angled to obtain a Doppler signal of maximal velocity while preserving a clear envelope. At each level of gradient, this angle was optimized by fine adjustment of the tilt of the hand-held transducer, guided only by the quality of the audio and spectral signals. No echocardiographic imaging was performed during the studies.

The Irex 3-B instrument had been modified by the addition of a DC coupler unit, which allowed simultaneous recording of pressure traces and Doppler spectral output on the 7-inch

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TABLE I Results

Parameter	r	SEE	n	Equation
Maximal Doppler vs maximal catheter	0.99	5.2	120	y = 0.98x + 0.7
Gradient > 100 mm Hg	0.98	4.6	17	y = 1.1x − 8.6
Gradient < 100 mm Hg	0.98	5.1	103	y = 0.95x + 2.1
Gradient <50 mm Hg	0.81	7.1	50	y = 0.7x + 10.6
Cardiac output >1.5 liters/min	0.97	8.0	78	y = 0.96x + 2.4
Cardiac output <1.5 liters/min	0.99	4.8	42	y = 0.94x + 4.9
Mean Doppler vs mean catheter	0.98	4.3	120	y = 0.94x + 2.9
Maximal Doppler vs peak-to-peak catheter	0.95	10.5	120	y = 0.89x + 1.8
Doppler-catheter (10-ms intervals)	0.95	9.4	2742	

SEE = standard error of the estimate.

strip-chart recorder. The Doppler spectral output and Millar pressure traces were recorded together with the lead II electrocardiogram at 100 mm/s. Cardiac output was measured by injecting indocyanine green in the left ventricle and sampling in the femoral artery.

The catheters were calibrated before use. Baseline records were then obtained at 0 gradient. The snare was next tightened to provide a gradient to aortic outflow. Once the dog had equilibrated at this gradient, new recordings were obtained. This was repeated for each level of obstruction created.

To derive gradient from the Doppler velocity, a simplification of the Bernoulli relationship was used: $P = 4V^2$, where P = pressure gradient at a specified time and V = simultaneous blood velocity. Since the transducer was angled to obtain maximum velocities, we assumed that the beam was nearly parallel to the jet. Furthermore, since the true direction of the aortic jet could not be known, we did not correct for possible angles between the Doppler beam and the jet.

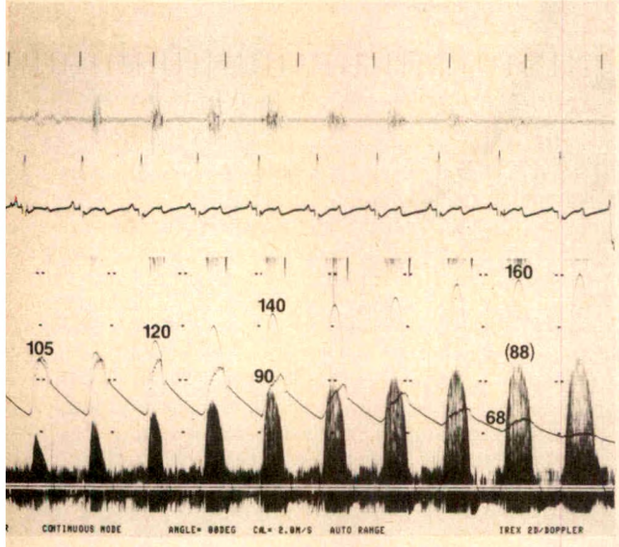


FIGURE 1. Record obtained at a paper speed of 25 mm/s during progressive tightening of the ascending aortic snare. **Vertical dots** are the Doppler velocity calibration in 2-m/s intervals. Peak left ventricular (LV) systolic pressures are recorded above the LV traces. Simultaneous aortic pressures are recorded next to the aortic traces. The maximal Doppler-derived gradient for the next to last cycle is recorded in parentheses next to the aortic pressure trace. Note the concurrent increase in both the catheter gradient and the Doppler velocity, on a beat-to-beat basis. At the start of the recording, peak LV systolic pressure is 105 mm Hg with a minimal gradient. At this point, the peak Doppler velocity is 1.7 m/s, which yields a maximal instantaneous gradient of 11 mm Hg. The snare is then tightened. Near the end of the recording, the maximal instantaneous catheter gradient is 92 mm Hg, with a peak LV systolic pressure of 160 mm Hg. The maximal Doppler velocity at this time is 4.7 m/s. This yields a maximal gradient of 88 mm Hg.

Data analysis: To determine the instantaneous relation between Doppler and catheterization data, selected beats were measured using a computer graphic analysis system consisting of a digitizing table (Houston Instruments) and a PDP 11/34 digital computer (Digital Computer Corp.). LV and ascending aortic pressure tracings were outlined, as was the envelope of the Doppler spectral signal. Data were acquired at 10-ms intervals throughout the LV ejection period. At each 10-ms interval, Doppler velocity was used to derive the pressure gradient by means of the simplified Bernoulli relation discussed previously. Mean Doppler gradient was calculated from the average of these gradients through the ejection period.

Linear regression analysis was done for the following pairs of data: (1) mean gradient (Doppler) vs mean gradient (catheter); (2) maximal pressure gradient (Doppler) vs maximal instantaneous gradient (catheter); (3) maximal pressure gradient (Doppler) vs peak-to-peak systolic gradient (catheter); (4) simultaneous Doppler-derived and catheter pressure gradients at 10-m/s intervals throughout the LV ejection period; and (5) ratio of time to peak Doppler velocity/LV ejection time vs maximal instantaneous and mean catheter gradient.

To determine where the outline of the Doppler signal should be traced, a random sample of 25 cycles was selected. Outlines were traced in 3 positions for each cycle: at the outer, "fuzzy" edge of the Doppler signal; through the center of the dark Doppler envelope; and at the inner border of the dark Doppler envelope.

Results

Satisfactory data were obtained from all dogs (Table I). Analysis was performed on 120 sinus beats selected at random from the 8 dogs. Beats with an indistinct or incomplete Doppler envelope were excluded, as were ectopic and postectopic beats. Cycles displaying pulsus alternans were included. The back-scattered Doppler signal recorded during indocyanine green dye injection was so markedly enhanced as to saturate the amplifier in the Doppler instrument. Therefore, no cycles recorded during or immediately after dye injection were included in this analysis.

Linear regression analysis of the mean Doppler-catheterization correlation (r) for the 25 cycles at 3 levels through the Doppler envelope yielded the following data (Fig. 2): outer edge: r = 0.96, standard error of the estimate (SEE) = 8.9 mm Hg; center of the dark envelope: r = 0.99, SEE = 4.4 mm Hg; inner border of the dark envelope: r = 0.99, SEE = 5.4 mm Hg. On this basis, we used the center of the dark Doppler envelope for all subsequent data analysis.

The maximal catheter gradients ranged from 4 to 179 mm Hg (mean 62.3). The Doppler peak velocity ranged from 1.1 to 6.5 m/s (mean 3.8). The cardiac output

ranged from 1.0 to 2.6 liters/min. The calculated aortic valve areas ranged from 0.1 to 2.0 cm^2.

The maximal instantaneous catheter gradient for each beat was compared with the Doppler-derived maximal gradient. The correlation was 0.99, with an SEE of 5.2 mm Hg (Fig. 3). The peak-to-peak catheter gradient correlated less well with the Doppler-derived maximal gradient and the SEE was greater: (r = 0.95, SEE = 10.5 mm Hg). For each beat analyzed, mean catheter gradients were compared with Doppler-derived mean gradients: r = 0.98, SEE = 4.3 mm Hg.

Separate linear regression analysis was performed for peak catheter gradients greater than and less than 100 mm Hg. For peak gradients greater than 100 mm Hg, r = 0.98, SEE = 4.6 mm Hg. For peak gradients less than 100 mm Hg, r = 0.98, SEE = 5.1 mm Hg. For the 50 points obtained at catheter gradients less than 50 mm Hg, the correlation was not as precise: r = 0.81, SEE = 7.1 mm Hg.

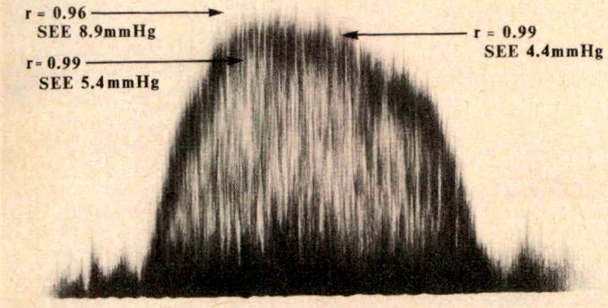


FIGURE 2. Schematic drawing of a Doppler signal. A dark "envelope" is at the outer margin of the signal. Above this envelope is a "fringe," which may represent noise. The 25 test records discussed in the Methods section were traced at the levels indicated in the diagram: outer margin of the Doppler signal, r = 0.96, standard error of the estimate (SEE) = 8.9 mm Hg; center of the dark envelope, r = 0.99, SEE = 4.4 mm Hg; inner edge of the dark Doppler envelope, r = 0.99, SEE = 5.4 mm Hg.

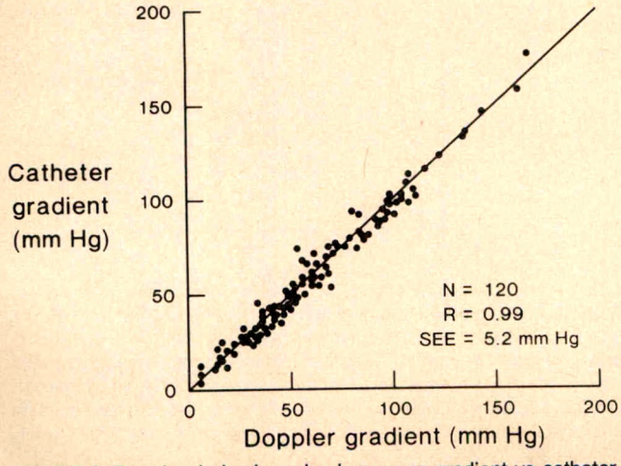
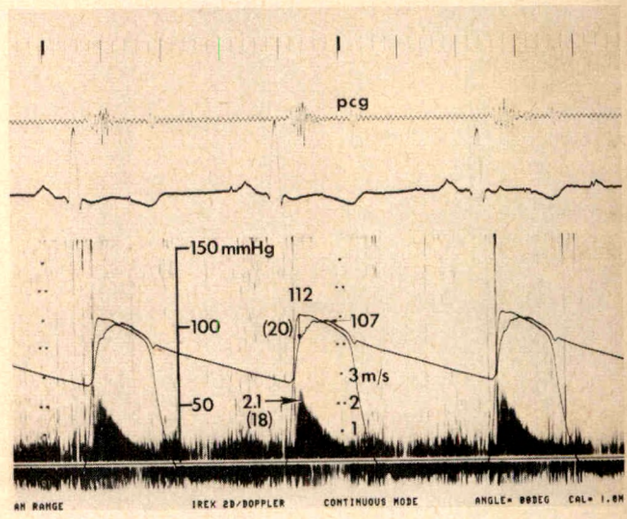


FIGURE 3. Doppler-derived maximal pressure gradient vs catheter-measured maximal instantaneous pressure gradient for all 120 points.

To examine the effect of cardiac output on the correlation, separate linear regression was performed on the maximal pressure gradient determined by Doppler and catheter for cardiac outputs greater than and less than 1.5 liters/min. For cardiac outputs greater than 1.5 liters/min, r = 0.97, SEE = 8 mm Hg; for those less than 1.5 liters/min, r = 0.99, SEE = 4.8 mm Hg.

The points obtained from digitization of the Doppler and catheterization data at 10-ms intervals were compared throughout the period of LV ejection. For the 2,742 points obtained from the 120 beats analyzed, the correlation was excellent (r = 0.95, SEE = 9.4 mm Hg) (Fig. 4 to 7).

No significant correlation (r = −0.01) was observed between the ratio of time to maximum Doppler veloc-



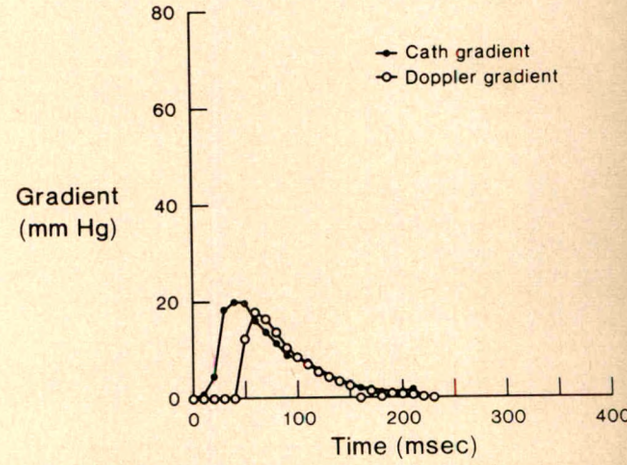


FIGURE 4. Top, record obtained at low gradient. The peak left ventricular systolic pressure (112 mm Hg) is displayed above the left ventricular pressure trace. The maximal instantaneous catheter gradient (20 mm Hg) is listed in parentheses next to the **vertical arrow.** The peak Doppler velocity (2.1 m/s) is displayed next to the Doppler signal. The gradient calculated from this (18 mm Hg) is listed in parentheses underneath the velocity. **Vertical dots** are the Doppler velocity calibration in 1-m/s intervals. Peak aortic pressure (107 mm Hg) is indicated by **thin horizontal arrow.** Note the discrepancy between the maximal instantaneous gradient (20 mm Hg) and the peak-to-peak catheter gradient (5 mm Hg). pcg = phonocardiogram. **Bottom,** digitized pressure gradient data obtained from the above record. Note the delay in initial upstroke seen in the Doppler trace.

ity/LV ejection time and maximal pressure gradient. Similarly, no significant correlation (r = 0.08) was found between the LV ejection time and peak pressure gradient.

Discussion

This study was undertaken in an idealized setting in order to examine the details of the Doppler-catheterization correlation freed from the technical limitations inherent in a clinical trial. Our findings identified a close correlation between Doppler-derived maximal gradient and maximal instantaneous catheter gradient. The relation was linear and remained so at the extremes of gradient, with somewhat less precise correlation observed for gradients less than 50 mm Hg. Among the explanations for this observation is that the velocity profile across mildly stenotic valves is less flat than for more severe stenoses, resulting in greater errors from neglecting the contribution of viscous friction to the gradient calculation. In addition, the slight error introduced by neglecting the prestenotic velocity may be more appreciable at low levels of gradient. At gradients greater than 120 mm Hg, the Doppler signal continued to reflect accurately the true pressure drop across the ascending aorta.

The correlation of mean gradients was essentially similar to that noted for maximal instantaneous gradients. This suggests that the relation between Doppler velocity and catheterization data applies not only at maximal gradient, but also during the entire period of ejection.

The point-to-point correlations were good, but appeared to be somewhat affected by a brief delay often seen in the Doppler record at the beginning and end of

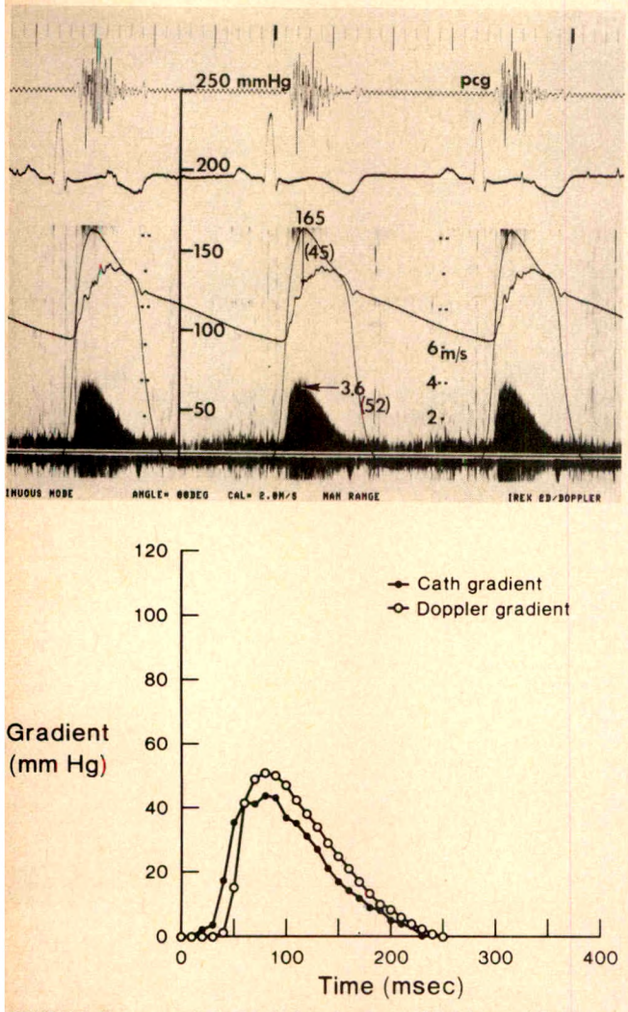


FIGURE 5. Top, record obtained at moderate gradient. Legend for Figure 4 provides explanation of the record. **Vertical dots** representing the Doppler velocity calibration are in 2-m/s intervals. The peak systolic left ventricular pressure was 165 mm Hg. Maximal instantaneous pressure gradient was 45 mm Hg. Maximal Doppler velocity was 3.6 m/s, yielding a calculated gradient of 52 mm Hg. **Bottom,** digitized pressure gradient data obtained from the above record. Doppler slightly overestimates the gradient in this instance.

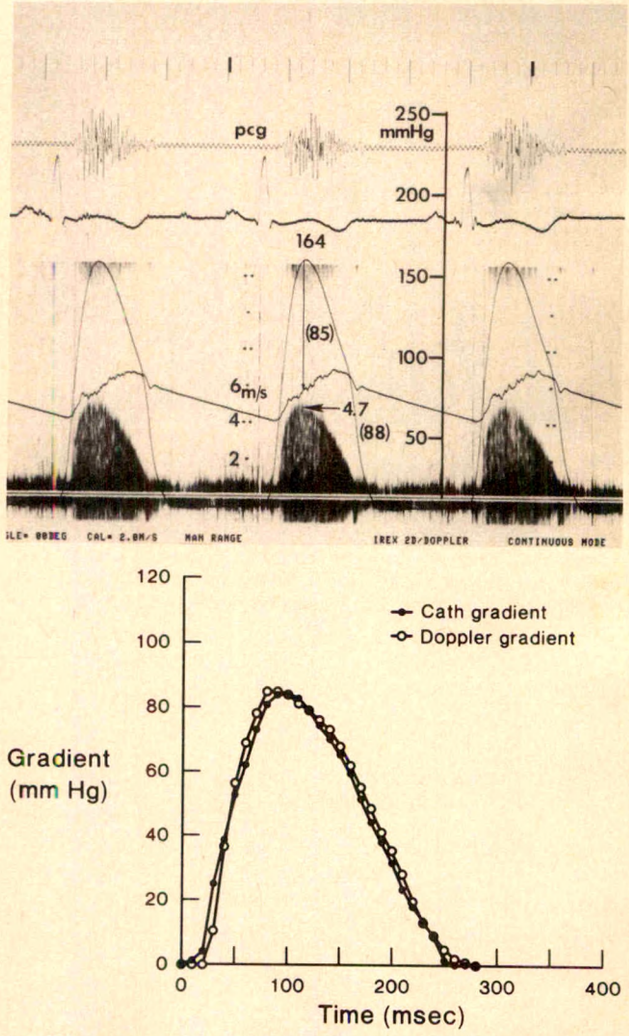
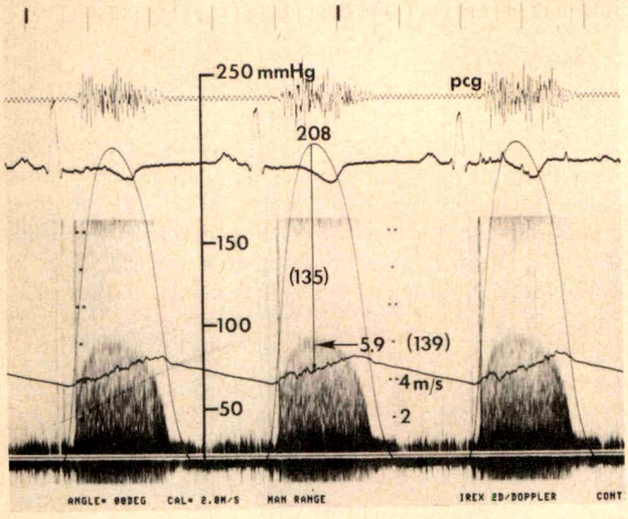


FIGURE 6. Top, record obtained at high gradient. Legend for Figure 4 provides explanation of the record. Peak systolic left ventricular pressure was 164 mm Hg. Maximal instantaneous pressure gradient was 85 mm Hg. Maximal Doppler velocity was 4.7 m/s, yielding a calculated gradient of 88 mm Hg. **Bottom,** digitized pressure gradient data obtained from the above record. The 2 curves correspond closely throughout systole.



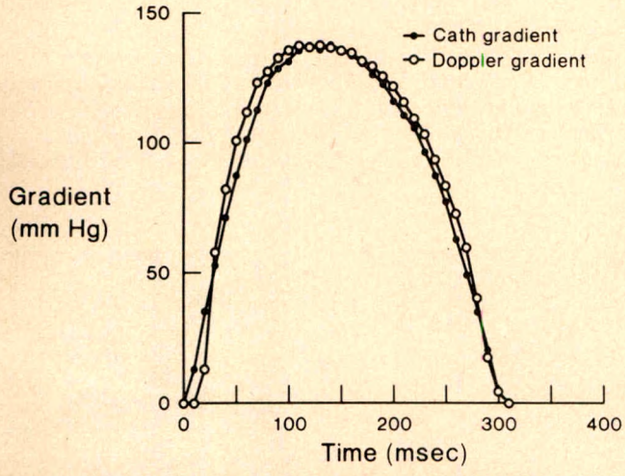


FIGURE 7. Top, record obtained at a critical gradient. See Figure 4 for an explanation of the record. Peak systolic LV pressure was 208 mm Hg. Maximal instantaneous pressure gradient was 135 mm Hg. Maximal Doppler velocity was 5.9 m/s, yielding a calculated gradient of 139 mm Hg. **Bottom,** digitized pressure gradient data obtained from the above record. The 2 curves correspond very closely and are essentially superimposed.

LV ejection, times when the pressure gradient was changing most rapidly. In a rapidly changing hydrodynamic system, the pressure waveform precedes the velocity pulse in time. In addition, the Chirp Z spectral analysis algorithm incorporated into the Doppler instrument used in this study introduces a small delay in the display in the returning Doppler signal. Neglecting the contribution of flow acceleration when deriving pressure gradients from the modified Bernoulli equation would also be expected to introduce a delay in the Doppler-calculated pressure curve.[5]

Despite these minor points, the close Doppler-catheterization correlation observed within the period of LV ejection strongly suggests that the Doppler signal accurately represents pressure gradients, from beat to beat and throughout LV ejection. Further, this correlation persists over a wide range of gradients.

The correlation between Doppler-derived maximal gradient and peak-to-peak systolic gradient determined at catheterization was good, but not as close as for the other variables discussed above. This is not surprising, because the Doppler signal measures instantaneous changes in blood velocity and would be expected to correspond most closely with instantaneous measurements of pressure gradient and not with nonsimultaneous points as represented by the expression of peak-to-peak gradient. Indeed, the use of the convenient catheterization laboratory measurement of peak-to-peak systolic gradient for correlation with Doppler pressure gradient may lead to the erroneous conclusion that the Doppler technique overestimates the severity of AS.

The lack of significant correlation between maximal and mean catheter gradient and the ratio of time to maximal Doppler velocity/LV ejection time contradicts previous clinical work.[5] This finding may be explained by the physiologic differences between acute LV outflow obstruction and the chronic obstruction observed in clinical situations. However, in recent studies in our clinical laboratory, similar observations regarding this lack of significant correlation have been independently confirmed.[6]

This study shows that accurate continuous-wave Doppler assessment of pressure gradients may be made solely by optimizing the audio and spectral signals, without incorporating angle correction. In this experimental model of aortic outflow obstruction, the Doppler-derived gradients correlated closely with catheter gradients throughout systole and across a wide range of obstruction.

Acknowledgment: We acknowledge Jerry D. Dewey, Vernon P. Weber and Curtis Grabau for their technical assistance; Robert M. Owen for computer programming; and Duane M. Ilstrup for statistical analysis.

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Dynamic Nature of Coronary Collateral Blood Flow

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How coronary collateral blood flow is "turned on" and "turned off" is not known. Moreover, the rapidity with which coronary blood flow can become evident after total occlusion of a coronary artery and then become nondetectable again after resolution of the coronary artery occlusion has been reported infrequently.[1,2] Recent studies[3,4] showed that collateral channel filling may improve within 60 to 90 seconds after sudden coronary occlusion by an angioplasty balloon in certain patients with severe coronary stenosis. This report demonstrates the dynamic nature of coronary collateral flow. Collateral blood flow appeared immediately after total occlusion of a coronary artery. After transluminal disobliteration,[5] anterograde blood flow returned and collateral blood flow was no longer seen.

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A 63-year-old man with a 5-month history of poorly controlled angina pectoris underwent left-sided cardiac catheterization and coronary arteriography. Left ventriculography revealed moderate apical hypokinesia with a normal ejection fraction of 67%. The initial coronary arteriographic injections (Fig. 1) revealed high-grade lesions in all of the proximal major branches of both coronary arteries. No left-to-right collateral filling was noted (Fig. 1B). Right coronary arteriography (Fig. 1A) revealed multiple lesions, including greater than 99% narrowing near its ostium with brisk distal flow. Subsequent injections of the right coronary artery after the onset of 5/10 chest pain revealed poor distal filling and evidence of reciprocating flow of unopacified blood from the distal artery. The chest pain was not responsive to sublingual or intracoronary nitroglycerin administration. Subsequently,

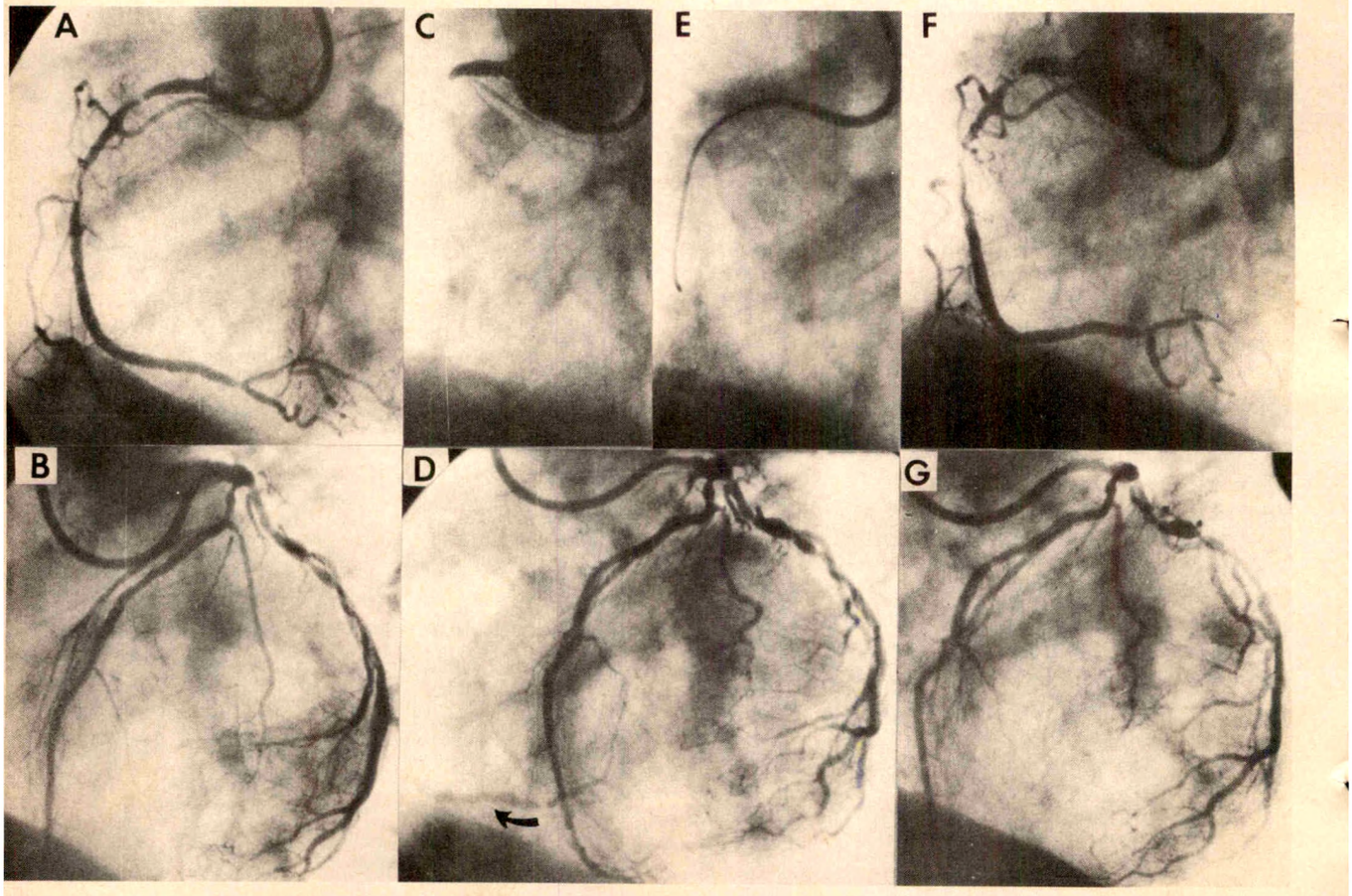

FIGURE 1. Selective injections of the right (**top**) and left (**bottom**) coronary arteries in the left anterior oblique projection. The injections are arranged in chronologic order before (**A** and **B**), during (**C, D** and **E**) and after (**F** and **G**) total occlusion of the proximal right coronary artery, and reveal collateral flow (**arrow, D**) while the right coronary artery is occluded.

injections revealed progression to total occlusion of the proximal vessel and no distal filling (Fig. 1C). An injection of the left coronary artery revealed multiple obstructions, as had been previously seen, but left-to-right collateral flow, which filled the right coronary artery, was noted (Fig. 1D). A guidewire was then passed through the occluded right coronary artery lesion and a catheter was passed over the wire but could not be advanced past the lesion (Fig. 1E). Subsequent injection of contrast medium revealed opening of the proximal right coronary artery obstruction with return of anterograde flow through the right coronary artery (Fig. 1F). A repeat left coronary arteriogram revealed disappearance of left-to-right collaterals (Fig. 1G). The chest pain was completely relieved concurrent with the restoration of flow through the right coronary artery, approximately 20 minutes after the onset of pain and the demonstration of sluggish flow in the right coronary artery. A 12-lead electrocardiogram at the completion of the catheterization study was unchanged from that before catheterization.

In the coronary care unit, the patient received full-dose heparin and antiplatelet therapy. He had a small increase in serum creatine kinase levels, to 321 mU/ml (normal 45 to 235 mU/ml) with 14.8% MB fraction. He later underwent successful coronary artery bypass surgery.

The ineffectiveness of sublingual and intracoronary nitroglycerin on the total occlusion of the proximal right coronary artery in our patient suggested that the occlusion may not have been a result of coronary artery spasm but may have been the result of either a platelet plug or an acute intracoronary thrombotic occlusion, which are known complications of coronary angiography.[6]

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Pacemaker Malfunction After Nitrous Oxide Anesthesia

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Entrapment of gas in the pacemaker pocket has been reported.[1,2] Pacemaker malfunction in those studies was a result of loss of anodal contact, and presented with small amplitude, variable amplitude or absent pacing spikes with loss of ventricular capture. We report a patient in whom pacemaker malfunction was caused by the presence of an anesthetic gas within the pacemaker pocket itself.

An 89-year-old woman was hospitalized after she was found lying on the floor of her home. An evaluation revealed both a fractured hip and complete heart block. A Telectronics 5281 (Optima MPT; VVI, M) generator and a unipolar Medtronic 4011-58 electrode were implanted. The prepectoral pocket was flushed with antibiotic solution before closing. The generator exhibited normal (VVI) function for 24 hours after implantation. The day after implantation the patient underwent total hip replacement with use of nitrous oxide and narcotic anesthesia. While in the operating room, intermittent failure to pace was noted. Examination of the pacemaker pocket revealed marked crepitus and distention owing to gas in the prepectoral pocket. Agitation of the pacemaker pocket with motion of the generator led to intermittent appearance of ventricular spikes and ventricular capture. Positioning a magnet over the generator led to VOO pacing at a rate of 99 beats/min without further loss of capture. The gas was manually expressed to the perimeters of the pocket and loss of ventricular capture became less frequent. The next day, crepitus in the prepectoral pocket could no longer be demonstrated, and motion of the generator did not lead to loss of ventricular capture.

Entrapment of gas in the pacer pocket with resultant pacer malfunction owing to interruption of anodal contact has been described.[1,2] In both previous cases, the involved gas was air that had not been effectively evacuated from the pacemaker pocket during the implant procedure. In the present case, the entrapped gas was a mixture of nitrous oxide and air.

Nitrous oxide is an inorganic anesthetic gas that is poorly soluble in water. It diffuses readily into the body's air-containing structures until it approaches equilibrium with the partial pressure of the inspired gas mixture. This phenomemon can lead to a marked volume increase of any air pockets, such as a pneumothorax, or even of intracranial air after pneumoencephalography.[3,4] In the present case, despite air evacuation with antibiotic solution before closure of the prepectoral pocket, a small amount of air remained entrapped in the generator pocket. In general, this small amount of air should have no clinical significance. However, nitrous oxide diffused into the pocket from the blood to reach an equilibrium with its partial pressure in the inspired gas mixture. This caused an expansion of the gas in the pocket, which led to loss of anodal contact and pacing system malfunction.

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Angiographic Diagnosis of Coronary Sinus Ostium Atresia

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Atresia of the ostium of the coronary sinus is a rare cardiac anomaly that has been diagnosed exclusively at necropsy.[1]

Cardiac catheterization of a term female infant confirmed the clinical and 2-dimensional echocardiographic diagnosis of pulmonary atresia with intact ventricular septum. Right ventricular angiography showed myocardial sinusoids with retrograde filling of the coronary arteries. The coronary veins drained to the left superior vena cava (SVC). There was no direct coronary venous drainage to either atrium. Selective injection into the left SVC (Fig. 1) confirmed the diagnosis of atresia of the coronary sinus ostium. The patient survived a palliative shunt but died of intraoperative arrhythmias at 3 months of age after attempted pulmonary valvotomy. Autopsy was refused.

A recent review by Gerlis et al[1] reported 15 cases of coronary sinus ostium atresia and persistent left SVC, all discovered at necropsy. Six cases had associated cardiovascular anomalies: most of the remainder were asymptomatic adults. We believe that the infant described herein is the first in whom coronary sinus ostium atresia was diagnosed using angiography and the first to have associated pulmonary atresia with intact ventricular septum.

On retrospective review, the echocardiogram showed the small left SVC but not the coronary sinus or coronary sinus ostium. Therefore, the only echocardiographic clue to the diagnosis was the absence of the dilated coronary sinus usually associated with a left SVC. Although not performed in our infant, Doppler interogation of the left SVC should reveal reversal of the usual direction of flow.

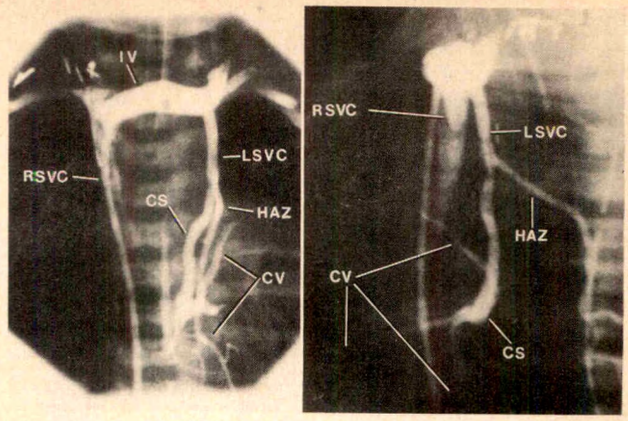

FIGURE 1. Selective left superior vena cava (LSVC) angiogram in a patient with atresia of the coronary sinus (CS) ostium shown in anteroposterior (**left**) and lateral (**right**) projections. Contrast filled the coronary veins (CV), LSVC, innominate vein (IV) and right superior vena cava (RSVC). No contrast entered either atrium. After injection, contrast was observed draining in a retrograde fashion from LSVC to IV to RSVC to right atrium. HAZ = hemiazygos vein.

Although this anomaly is believed to be of little functional significance,[2] diagnosis may be important before the surgical correction of associated cardiovascular abnormalities. A persistent left SVC and innominate vein recognized during preparation for cardiopulmonary bypass may be clamped or ligated.[3] Interruption of the sole route of cardiac venous return could have disastrous consequences such as ischemia or coronary arterial or venous thrombosis.

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Contrast-Enhanced Cine Computed Tomography for Diagnosis of Right Coronary Artery to Coronary Sinus Arteriovenous Fistula

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DONALD CLARK, MD

Until recently, computed tomography (CT) could not be applied to the heart because of relatively slow exposure speeds of 1 to 5 seconds, which is not long enough to achieve adequate temporal resolution. With the development of the Cine/CT C-100® scanner (Imatron), multilevel 50-ms exposures can be obtained using peripheral intravenous bolus injections of contrast medium for image enhancement.[1] Resolution of cardiac anatomy in transverse 8-mm slices may provide diagnostic information not available by other techniques. The CT findings of a large right coronary artery to coronary sinus arteriovenous fistula are presented.

A 54-year-old man who had been followed for "mild" valvular heart disease for 10 years was admitted for evaluation of squeezing midsternal chest pressure radiating to the left arm, associated with dyspnea and provoked by physical exertion or psychological stress. Rest or nitroglycerin relieved the pain. The radial pulse was 54 beats/min and regular, and blood pressure 140/90 mm Hg in both arms, supine. There was no neck vein distention at 30° and the carotid pulses were normal. The cardiac apex impulse was in the sixth space in the anterior axillary line. There was a systolic left ventricular lift. The first heart sound was normal. The second heart sound was split but not fixed. A harsh grade 3/6 pansystolic murmur heard loudest in the sitting postion at the third left sternal border was increased by squatting and decreased with standing and Valsalva maneuver. A grade 2/6 diastolic decrescendo murmur was heard best at the same location. There were no gallops. An electrocardiogram revealed sinus bradycardia (52 beats/min), unifocal ventricular premature complexes, left anterior hemiblock and nonspecific ST-T abnormalities. There was mild cardiomegaly by chest radiograph. Echocardiography revealed slight left ventricular dilatation. First-pass radionuclide angiography

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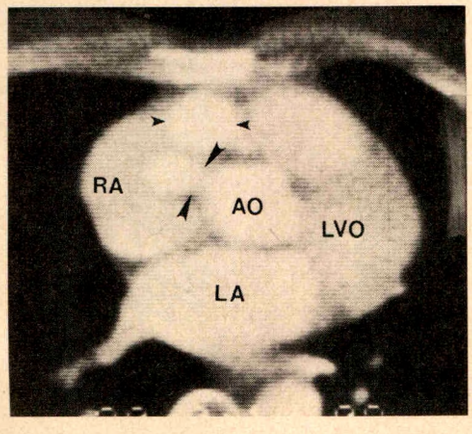

FIGURE 1. Cine CT C-100® scan at the level of the right coronary ostium. **Large arrows** mark the proximal right coronary artery arising from the aorta (AO) and **small arrows** mark a more distal segment. LA = left atrium; LVO = left ventricular outflow tract; RA = right atrium.

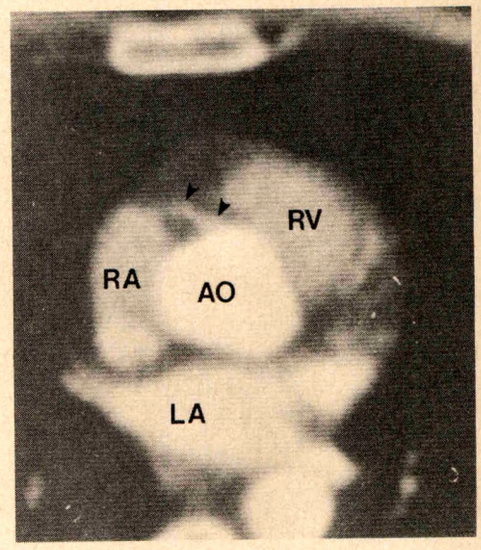

FIGURE 2. Cine CT C-100® scan showing origin and proximal segment of a normal right coronary artery (**arrows**). AO = aorta; LA = left atrium; RA = right atrium; RV = right ventricle.

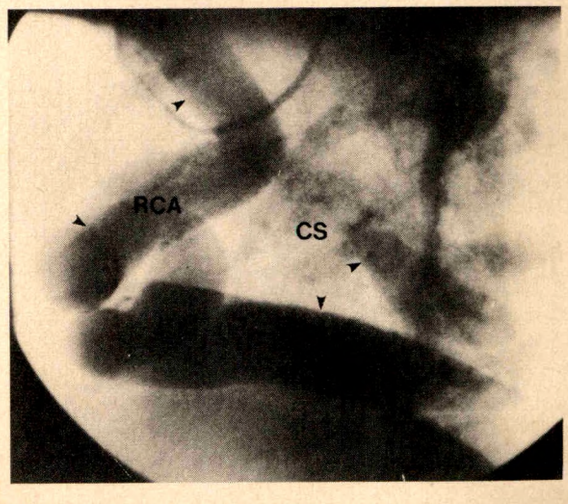

FIGURE 3. Selective injection of proximal right coronary artery (RCA) in left anterior oblique 60° projection. Note the markedly dilated and tortuous vessel (**arrows**), whose distal segment enters the coronary sinus (CS).

disclosed normal right and left ventricular ejection fractions with an unexplained concentration of tracer activity outside the right heart border. A treadmill stress test was stopped at 4 minutes owing to chest pain, but ST segments were nondiagnostic owing to ST-T abnormalities at rest. Cine-CT scan in the transverse plane at the level of the origins of the coronary arteries revealed a dilated right coronary artery (RCA) (1.4 cm in diameter) arising from the aorta (Fig. 1), as contrasted with a normal RCA (Fig. 2). Contiguous slices below the level of the origin of the RCA revealed the dilated RCA in its middle and distal segments, but the specific entry point into the coronary sinus was not seen. Analysis of flow curves demonstrates early reappearance in the right atrium and ventricle. CT scan also disclosed mild dilatation of the main pulmonary artery and left atrium. Cardiac catheterization revealed normal right and left ventricular function with no valvular heart disease. The left coronary artery was normal. The RCA arose from the normal location in the aorta but was enlarged and tortuous, eventually communicating with the coronary sinus (Fig. 3). A left-to-right shunt at the right atrial level was 1.3:1.

The Cine/CT C-100 scanner has been shown previously to visualize segments of the coronary arteries[2] and saphenous vein bypass grafts,[3] although sufficient image resolution does not yet exist to detect atherosclerotic narrowing. This report illustrates the contribution of the Cine/CT C-100 scanner to provide information not available using other noninvasive methods for the diagnosis of an uncommon congenital anomaly,[4,5] which caused clinical symptoms of angina pectoris.

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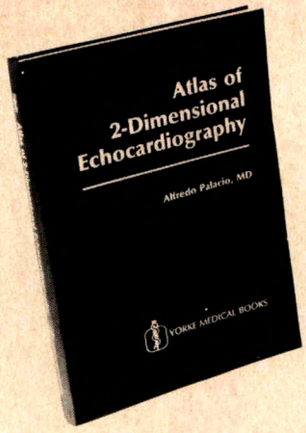

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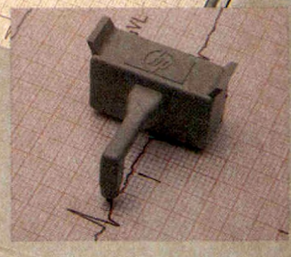

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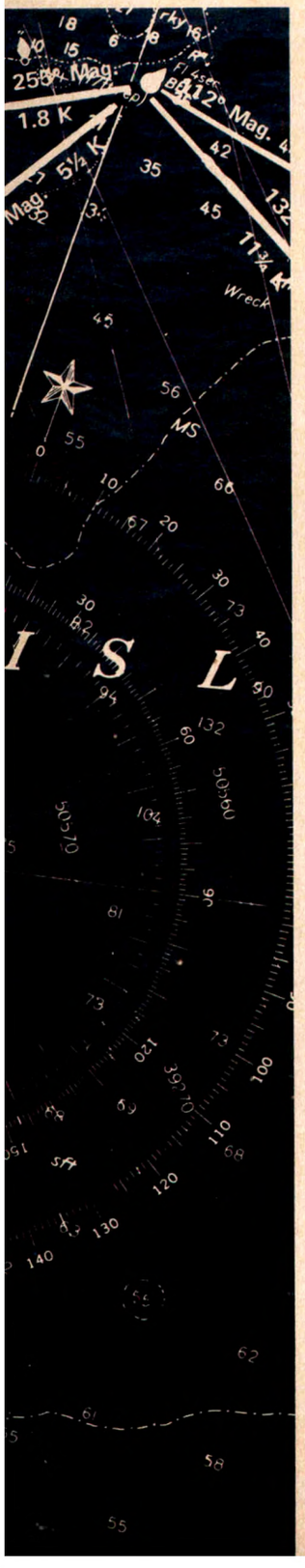
Initial therapy should star on the right course.

hypertensive patients



Minipress® for initial therapy
(prazosin HCl)

- Is effective when used alone
- Does not cause a significant incidence of sexual impotence, although it has been reported[1]
- Does not adversely affect blood lipids*[2]
- Does not lower heart rate, cardiac output or work capacity[3]
- Does not induce potassium wasting[1]
- Most common side effects with Minipress, generally mild and transient, are dizziness, headache, drowsiness, palpitations, and nausea. Syncope (sudden loss of consciousness) has been reported in about 0.15% of patients at the recommended initial dose of 1 mg.

*Minipress is not indicated for the treatment of hyperlipidemia.

Minipress®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

for Initial Therapy in Hypertension

Please see Minipress brief summary on following page

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Minipress®
(prazosin HCl) Capsules 1mg, 2mg, 5mg

Brief Summary
MINIPRESS® (prazosin hydrochloride) Capsules ***For Oral Use***
INDICATIONS: MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.
WARNINGS: Minipress may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120–160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution. (See DOSAGE AND ADMINISTRATION.) Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.
If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.
Patients should always be started on the 1 mg capsule of MINIPRESS. The 2 and 5 mg capsules are not indicated for initial therapy.
More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure; namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.
Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS in pregnancy has not been established. MINIPRESS is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of MINIPRESS in children.
ADVERSE REACTIONS: The most common reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.
The following reactions have been associated with MINIPRESS some of them rarely. (In some instances exact causal relationships have not been established.)
Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular: edema, dyspnea, syncope, tachycardia.
Central Nervous System: nervousness, vertigo, depression, paresthesia.
Dermatologic: rash, pruritus, alopecia, lichen planus.
Genitourinary: urinary frequency, incontinence, impotence, priapism.
EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.
Other: diaphoresis.
Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances the exact causal relationship has not been established because the baseline observations were frequently inadequate.
In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.
DOSAGE AND ADMINISTRATION: The dose of MINIPRESS should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:
Initial Dose: 1 mg two or three times a day. (See WARNINGS.)
Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.
Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.
OVERDOSAGE: Accidental ingestion of at least 50 mg of MINIPRESS in a two year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.
Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate MINIPRESS is not dialysable because it is protein bound.
TOXICOLOGY: Testicular changes, necrosis and atrophy have occurred at 25 mg/kg/day (60 times the usual maximum recommended dose of 20 mg per day in humans) in long term (one year or more) studies in rats and dogs. No testicular changes were seen in rats or dogs at the 10 mg/kg/day level (24 times the usual maximum recommended dose of 20 mg per day in humans). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS (prazosin hydrochloride) therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on MINIPRESS (prazosin hydrochloride) alone for up to 51 months did not demonstrate changes in sperm morphology suggestive of drug effect.
HOW SUPPLIED: MINIPRESS is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).
More detailed information available on request.

References: 1. Pitts NE: The clinical evaluation of prazosin, a new antihypertensive agent, in Prazosin Clinical Symposium Proceedings. Published as a special report by *Postgraduate Medicine*, New York, McGraw-Hill Book and Education Services Group, 1975, pp 117-127. **2.** Adapted from Kaplan NM: Summary: *J Cardiovasc Pharmacol* 4 (suppl 2): S265, 1982. **3.** Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in Prazosin Clinical Symposium Proceedings. Published as a special report by *Postgraduate Medicine*, New York, McGraw-Hill Book and Education Services Group, 1975, pp 45-52.

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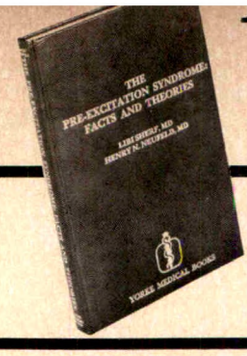

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC
Henry N. Neufeld, MD, FACC

1978, 288 PAGES, 110 ILLUS., 1,000 REF.

Every Cardiologist, Internist, Pediatrician, Surgeon — Indeed, *Every Physician* — Should Have a Good Basic Knowledge of The Pre-excitation Syndrome. Here Are Just a Few Reasons Why This is so Essential:

- ⅓ of all pre-excitation cases are misdiagnosed.
- 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies on patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals

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7. Prognosis
8. Treatment
9. Problems of Diagnosis — Some Illustrative Cases
10. Summary of Findings and Theories of Pre-excitation Syndrome
11. Concept of Interacting Structural and Functional Factors
12. Explanation of Some Phenomena of the Pre-excitation Syndrome by the Proposed Concept
13. Various QRS Patterns in the Different Forms of Pre-excitation

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Journal: Harvey W, Heberden W, Withering W, Stokes W, Murrell W, Einthoven W, Osler W. Anomalies and curiosities of cardiology and of cardiologists. Reflections of famous medical Williams. Am J Cardiol 1984;53:900–915.

Chapter in Book: Cabot RC, White PD, Taussig HB, Levine SA, Wood P, Friedberg CK, Nadas AS, Hurst JW, Braunwald E. How to write cardiologic textbooks. In: Hope JA, ed. A Treatise on Disease of the Heart and Great Vessels. London: Yorke Medical Books, 1984;175–200.

Book: Carrel A, Cutler EC, Gross RE, Blalock A, Craffoord C, Brock RC, Bailey CP, DeBakey ME. The Closing of Holes, Replacing of Valves and Inserting of Pipes, or How Cardiovascular Surgeons Deal with Knives, Knaves and Knots. New York: Yorke University Press, 1984:903.

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The AJC in December 1960

WILLIAM C. ROBERTS, MD

The AJC in December 1960 contained 27 articles, including a symposium on monoamine oxidase inhibitors, occupying 149 pages. This piece will comment on 1 article.

Brockenbrough and Braunwald[1] from Bethesda, Maryland, described a technique for introducing a catheter by the percutaneous method across the atrial septum, allowing angiography with injection of contrast material into either the left atrium or the left ventricle. Percutaneous puncture of the right femoral artery was carried out with a #16 gauge needle. A flexible coiled spring guide was then passed into the vein through the needle and then the needle was removed. A radioopaque polyethylene catheter 70 cm in length with an internal diameter of 1.15 mm and an outer diameter of 2.30 mm and with a curved distal end was introduced over the guidewire and advanced well into the femoral vein. The guidewire was then withdrawn. To straighten the loop and to facilitate placing the catheter in the right atrium, a stylet of 19-gauge hypodermic tubing, 5 mm shorter than the catheter, was inserted into and advanced with the catheter. After the catheter was positioned in the right atrium, the stylet was replaced by a 19 gauge transseptal needle, 71 cm in length. When the catheter and the needle had been appropriately positioned against the fossa ovale portion of the atrial septum, puncture of the septum was achieved by advancing the needle tip. Entry into the left atrium was confirmed by pressure measurements and the free withdrawal of oxygenated blood. The catheter was then advanced with the needle until both were within the left atrium. The catheter was then slipped over the held-steady needle and directed into the left ventricular cavity. The needle was then withdrawn. The left ventricular pressure was recorded and, if indicated, angiography performed. With this technique it made possible the performance of both right- and left-sided cardiac catheterizations using the same percutaneous puncture.

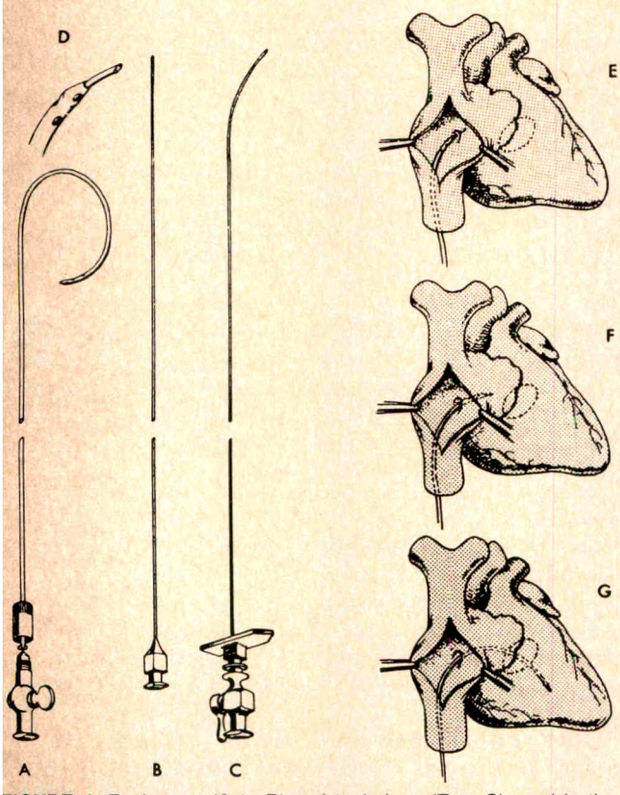
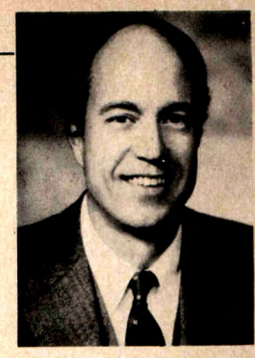


FIGURE 1. Equipment (**A** to **D**) and technique (**E** to **G**) used in the percutaneous method of transseptal left-sided cardiac catheterization. Reproduced with permission of the publisher.

Reference

1. **Brockenbrough EC, Braunwald E.** A new technique for left ventricular angiography and transseptal left heart catheterization. Am J Cardiol 1960;6:1062–1064.



Some Good Cardiologic Books

Most publishers of medical books send recently published books to editors of medical journals in hopes that their books will be reviewed, and, of course, reviewed favorably. During my 42-month tenure as editor of AJC, no book reviews have appeared, although recently received books are listed in the *Journal* about every 3 months. Picking the best of the medical books each year obviously is difficult. What is "best" to one person is not necessarily "best" to another. This piece lists a few of the better books that have crossed my editor's desk in 1985.

1. Braunwald E, editor *Heart Disease. A Textbook of Cardiovascular Medicine.* 2nd ed., Philadelphia: WB Saunders Company, 1984:1943, $95.00.

2. Hurst JW, ed. *The Heart, Arteries and Veins.* 6th ed., New York: McGraw-Hill Book Company, 1986:2193, $92.00.

These are the 2 most important books that a cardiologist can own. Because the subject matter in each book is written by different authors and because the material in each book is organized and presented quite differently, it is advantageous to own both books. Since each has a new edition every 3 years, it would appear most reasonable to purchase 1 book 1 year and the other book when its new edition appears.

The magnitude of the information presented in these 2 books is astounding and a tribute to the writing and organizational skills of the 2 editors. The Braunwald book weighs 4,380 grams, contains 1,943 pages with a maximum of 1,050 words per page, 57 chapters (25 of which were authored or coauthored by Braunwald) written by 51 authors, 15,112 references, 1,193 figures and 252 tables. The Hurst book weighs 3,260 grams, contains 2,193 pages with a maximum of 850 words per page, 140 chapters (8 of which were authored or coauthored by Hurst) written by 183 authors, 11,083 references, 1,005 figures and 199 tables.

3. Kirklin JW, Barratt-Boyes BG. *Cardiac Surgery. Morphology, Diagnostic Criteria, Natural History, Techniques, Results, and Indications.* New York: John Wiley & Sons, 1986: 1572, $150.00.

Absolutely magnificent book! As Dwight McGoon says in the foreword: "Perhaps you are like me in having fancied at one time or another of someday being able to encompass the entire body of essential information of a selected specialty and then 'wrap it up' into a skillfully coordinated, comprehensive, concise compendium. Increasingly rare are the occasions when that fantasy can be transformed into reality. Indeed, for cardiac surgery, such an accomplishment may never again occur after this book. This is especially true if an aspiring author is also required to be a principal contributor to essentially every frontier of progress in the entire specialty. Thus, from its very inception, this book has been unique. . . . The entire expanse of cardiac surgery seems to be here, laid out in the same crisp, logical, fully documented style that we have all come to recognize and respect in the many other reports, lectures, and publications provided by these particular authors."

This book has only 2 authors and each chapter reflects their combined outstanding authority on that subject. This book is a must for all physicians and surgeons involved in caring for persons with cardiac disease. It is one of the very best medical books ever published! I confidently predict that another edition of it will never appear. It is a classic from the beginning.

4. Crawford ES, Crawford, JL. *Diseases of the Aorta Including an Atlas of Angiographic Pathology and Surgical Technique.* Baltimore: Williams & Wilkins, 1984: 401, $135.00.

It is ideal, of course, when *the* recognized authority in a field authors a book on his (her) area of expertise. Such is the case in the above book. "Diseases of the Aorta" is primarily an atlas with magnificent color drawings by Perrin Sparks Smith. The drawings depict most aortic diseases, their varying appearances, and the techniques available for their surgical treatment. Although the book lacks computed tomography and echocardiographic observations, it nevertheless is masterful and should be owned by all surgeons who operate on patients with aortic disease. What pride the senior author must feel for his son to be a coauthor.

5. Wilcox BR, Anderson RH. *Surgical Anatomy of the Heart*. New York: Raven Press (published by special arrangement with Gower Medical Publishing), 1985: 148, $55.00.

This book is a color atlas combining photographs of normal and congenitally malformed hearts with accompanying color and line diagrams with appropriate text. The book combines efforts of a cardiac surgeon (Ben Wilcox) and a cardiac morphologist (Bob Anderson). The result is a splendid book. It actually concerns only the normal and the congenitally malformed heart and therefore its title is not fully descriptive of its contents. This book should be in the library of surgeons who operate on patients with anomalies of the heart and great vessels.

6. King SB III, Douglas JS Jr. *Coronary Arteriography and Angioplasty*. New York: McGraw Hill Book Company, 1985:478, $70.00.

Spencer King and John Douglas have lived in the cardiac catheterization laboratory for a number of years, the last 5 of which were working with the late Andreas Gruentzig, and this book shows that they know what they were doing.

7. Cohn PF, editor. *Diagnosis and Therapy of Artery Disease*. 2nd ed. Boston: Martinus Nijhoff Publishing, 1985:517, $69.50.

8. Connor WE, Bristow JD, editors. *Coronary Heart Disease. Prevention, Complications and Treatment*. Philadelphia: J.B. Lippincott, 1985:461, $45.00.

9. Califf RM, Wagner GS, editors. *Acute Coronary Care, Principles and Practice*. Boston: Martinus Nijhoff Publishing, 1985:556, $52.50.

All 3 books are multiauthored with inherent advantages and disadvantages of each. None of these should be purchased until both the Braunwald and Hurst books have been bought.

10. Ellestad MH. *Stress Testing. Principles and Practice*. 3rd ed. Philadelphia: FA Davis Company, 1986: 564, $48.00.

Almost certainly the best book on this subject.

11. Feigenbaum H. *Echocardiography*. 4th ed. Philadelphia: Lea & Febiger, 1986:685, $55.00.

The first edition of this classic appeared in 1972 and a new edition has appeared every 4 or 5 years since. This new edition contains more 2-dimensional echocardiograms and also a good number of Doppler echocardiograms. This is the first echo book to buy.

12. Nanda NC, editor. *Doppler Echocardiography*. New York: Igaku-Shoin, 1985:522, $55.00.

An authoritative up-to-date book on a rapidly expanding subject.

13. Wenger NK, Hellerstein HK, editors. *Rehabilitation of the Coronary Patient*. 2nd ed. New York: John Wiley & Sons, 1984:563, $37.50.

14. Pollock ML, Schmidt DH, editors. *Heart Disease and Rehabilitation*. 2nd ed. New York: John Wiley & Sons, 1986:788, $47.50.

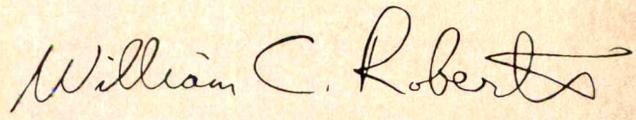
Two good and different multiauthored books on an important subject. I also like the book: Peterson LH. *Cardiovascular Rehabilitation. A Comprehensive Approach*. New York: MacMillan, 1983:363, $48.00.

15. Zipes DP, Jalife J, editors. *Cardiac Electrophysiology and Arrhythmias*. Orlando: Grune & Stratton, 1985:567, $98.50.

A book honoring Gordon K. Moe and having 174 contributors.

16. Freedom RM, Culham JAG, Moes CAF. *Angiocardiography of Congenital Heart Disease*. New York: MacMillan, 1984:691, $125.00.

Surely the best book on this subject.



William C. Roberts, MD
Editor-in-Chief

LETTERS*

THE ORIGIN OF GIANT U WAVES

Giant repolarization waves such as those reported by Shimoni et al[1] are virtually pathognomonic of a preceding syncope.[2] They may be indistinguishable from similar waves occasionally seen in Romano-Ward syndrome, with similar postsyncopal alternans.[3,4] I would suggest that the striking electrocardiographic abnormalities reported by Shimoni et al are more likely to have been caused by neural mechanisms than by the modest electrolyte disturbance documented after the patient's syncope. The electrolyte-dependent QT-interval prolongation, admittedly, provoked the torsades de pointes observed, with syncope; but the ultimate electrocardiographic appearances should have been attributed to syncope itself.

George Nikolic, MD
Canberra, A.C.T., Australia
9 January 1985

1. **Shimoni Z, Flatau E, Schiller D, Barzilay E, Kohn D.** Electrical alternans of giant U waves with multiple electrolyte deficits. Am J Cardiol 1984;54:920–921.
2. **Schamroth L.** The Disorders of Cardiac Rhythm. Oxford: Blackwell, 1971:177.
3. **Sharma S, Nair KG, Gadekar HA.** Romano-Ward prolonged QT syndrome with intermittent T wave alternans and atrioventricular block. Am Heart J 1981;101:500–501.
4. **Rennie JM, Arnold R.** Asystole in the prolonged QT syndrome. Arch Dis Child 1984;59:571–584.

REPLY: Giant repolarization waves, as described in our case report, are indeed indistinguishable from similar waves seen in Romano-Ward syndrome with postsyncopal alternans. However, these waves are not exclusively pathognomonic of a preceding syncope. Lopez et al[1] stated that "aside from the T wave alternans that appears in the congenital long Q-T syndrome, the acquired alternans has been observed in various clinical situations." Most of these "situations" are virtually low-serum electrolyte levels such as hypocalcemia, hypokalemia or hypomagnesemia. Schamroth[2] described giant repolarization waves (but without alternans) after recurrent syncopal attacks in patients with organic heart disease. Our patient had no evidence of organic heart disease when she entered the hospital, nor when she left it. Her striking electrocardiographic abnormalities regressed concomitantly with the gradual normalization of serum electrolyte levels.

As for the electrolyte levels (calcium = 6.5 mg/dl; potassium = 2.9 mEq/liter), most of the cases reviewed were reported to have T-wave alternans in association with milder electrolyte deficiencies.[1,3–6] Moreover, Mullican and Fisch[7] reported a case of giant U waves with postextrasystolic alternans that he believed was due to potassium depletion, despite a low-normal serum potassium level (3.7 mEq/liter). He suggested that the electrocardiographic changes may be a poor index of the plasma level of potassium. In conclusion, (1) postsyncopal giant U waves without alternans are seen in patients with organic heart disease; (2) postsyncopal alternans of giant repolarization waves occurs in Romano-Ward syndrome, but has not been described in patients without any organic heart disease; (3) the occurrence of episodic T (or U)-wave alternans in various clinical conditions suggests that several mechanisms may be involved[8]; and (4) electrolyte disturbances may cause giant U-wave alternans even in the absence of organic heart disease, as described in our case report.

Zvi Shimoni, MD
Edith Flatau, MD
Afula, Israel
25 February 1985

1. **Lopez FN, Cinca J, Sanz G, Periz A, Margina J, Betrin A.** Isolated T wave alternans. Am Heart J 1978;95:369–374.
2. **Schamroth L.** The disorders of cardiac rhythm. Oxford:Blackwell, 1971:177.
3. **Kimura E, Yoshida K.** A case showing electrical alternans of the T wave without change in the QRS complex. Am Heart J 1963;65:391–395.
4. **Bashour T, Rios JC, Forman PA.** U wave alternans and increased ventricular irritability. Chest 1973;64:377–383.
5. **Dolara A, Pozzi L.** Electrical alternation of T waves without change in QRS complex. Br Heart J 1971;33:161–163.
6. **Luomanmaki K, Keikkila J, Hartikainen U.** T wave alternans associated with heart failure and hypomagnesemia in alcoholic cardiomyopathy. Eur J Cardiol 1975;3:167–170.
7. **Mullican WS, Fisch C.** Postextrasystolic alternans of the U wave due to hypokalemia. Am Heart J 1964;68:383–386.
8. **Schwartz PJ, Malliani A.** Electrical alternans of the T wave: clinical and experimental evidence of the relationship with the sympathetic nervous system and with the long Q-T syndrome. Am Heart J 1975;89:45–50.

ICE-WATER WASHCLOTH RATHER THAN FACIAL IMMERSION (DIVING REFLEX) FOR SUPRAVENTRICULAR TACHYCARDIA IN ADULTS

We read the letter of Sacks and Smith[1] in which they described ice-water washcloth treatment of supraventricular tachycardia (SVT) in infants. At about the same time we read the letter, we treated a 45-year-old man in whom SVT developed. When we saw him in the emergency room the SVT (rate 180 beats/min), which he experienced for the first time, had lasted for about 2 hours and he had received no treatment. We tried the "diving reflex" as the initial treatment. When the patient sat up in bed for facial immersion many artifacts appeared on the monitor screen. To avoid these artifacts, a washcloth was immersed in ice-water for several minutes, wrung-out and applied to the patient's face after he assumed the recumbent position. The patient was instructed to hold his breath in inspiration. Twenty seconds later sinus rhythm appeared on the monitor screen and on the electrocardiographic strip. SVT did not recur. Prophylactic verapamil was prescribed and he was discharged 24 hours after the episode. This experience suggests that an ice-water cloth applied for a brief period to the face of an adult with SVT may safely and effectively restore sinus rhythm.

Sedat Tavşanoğlu, MD
Edip Özenel, MD
Istanbul, Turkey
4 February 1985

1. **Sacks LM, Smith RM.** Ice-water washcloth rather than facial immersion (diving reflex) for supraventricular tachycardia in infants [letter]. Am J Cardiol 1984;53:988.

POSTEXTRASYSTOLIC POTENTIATION DURING ACUTE MYOCARDIAL INFARCTION: PREDICTING PRESENCE OF VIABLE MYOCARDIUM

The study of Hodgson et al[1] suggests that postextrasystolic potentiation (PESP) may be useful during acute myocardial infarction (AMI) as a marker of ischemic but viable myocardium that may be salvaged by reperfusion. However, data from our laboratory[2] suggest alternative explanations of their findings. First, Figure 2 in their study implies that as a group, the ischemic segments had greater PESP than nonischemic segments. Although raw data are not presented, it appears that the function of some of the nonischemic segments may have deteriorated with premature stimulation. These findings have not been observed in experimental preparations using sonomicrometers[3] and 2-dimensional echocardiography[4] and suggest that the results observed by Hodgson et al may have been importantly influenced by the normalized floating axis angiographic analysis of endocardial motion used by the investigators.

Second, their method of regional analysis divided the ventricle into 3 large areas, which may have concomitantly embraced both ischemic and nonischemic zones. Because the study was of ventricular function only, conclusions regarding the state of ischemia of myocardium demonstrating PESP can only be inferred. Was this myocardium truly ischemic and did salvage of it by reperfusion account for the late return of function observed? "Tethering" or dyskinesia of nonischemic regions adjacent to ischemic regions has been well described in experimental animals[5] and humans.[6] Our study, which used contrast 2-dimensional echocardiography to delineate the region at risk, also demonstrated tethering of nonischemic myocardium and, furthermore, localized the PESP response to these regions. PESP was

* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

ost in the central 50% of the region at risk ıfter only 5 minutes of ischemia and was lost n the remainder of the region at risk after 30 minutes of ischemia. From 30 minutes on, he only dyssynergic regions demonstrating PESP were the nonischemic, nonjeoparlized regions bordering the infarct zone. This is not to say that ischemic myocardium annot show persistent PESP[4]; however, the everity of ischemia in these regions is probbly no worse than moderate and may not e of sufficient degree to produce significant nfarction. In any case, such myocardium ccupies only a small minority of the region t risk in the usual canine infarction. Most f the region at risk of AMI, even though till viable, did not demonstrate PESP in ur study. Our data suggest caution in aplying PESP to determine whether patients re candidates for an intervention during AMI.

Finally, our analysis of the tethered nonschemic adjacent zones suggests an alternaive explanation for the late improvement in egions demonstrating PESP during AMI een by Hodgson et al.[1] We found a tendency for improvement in unstimulated systolic hickening in tethered zones over the 6-hour uration of our experiment. These data sugest that the late improvement in function een by Hodgson et al was not necessarily ue to salvage of ischemic myocardium but ıay reflect a natural tendency of dysfuncional tethered myocardium to improve inependent of intervention.

Thomas Force, MD
Andrew J. Kemper, MD
Alfred F. Parisi, MD
West Roxbury, Massachusetts
28 January 1985

. **Hodgson JM, O'Neill WW, Laufer N, Bourdillon PDV, Walton JA, Pitt B.** Assessment of potentially salvageable myocardium during acute myocardial infarction: use of postextrasystolic potentiation. Am J Cardiol 1984;54:1237–1244.
. **Force T, Kemper AJ, Cohen C, Parisi AF.** Early loss of post-extrasystolic potentiation in acutely ischemic myocardium. Circulation 1985;71:602–609.
. **Crozatier B.** Relations between myocardial blood flow and postextrasystolic potentiation in epicardial and endocardial left ventricular regions early after coronary occlusion in dogs. Circulation 1982;66:938–944.
. **Sakamaki T, Corday E, Meerbaum S, Torres MAR, Fishbein MC, Y-Rit J, Aosaki N.** Relation between myocardial injury and postextrasystolic potentiation of regional function measured by two-dimensional echocardiography. JACC 1983;2:52–62.
. **Kerber RE, Marcus ML, Ehrhardt J, Wilson R, Abboud F.** Correlation between echocardiographically demonstrated segmental dyskinesis and regional myocardial perfusion. Circulation 1975;52:1097–1104.
. **Weiss JL, Bulkley BH, Hutchins GM, Mason SJ.** Two-dimensional echocardiographic recognition of myocardial injury in man: comparison with postmortem studies. Circulation 1981;63:401–408.

REPLY: The intent of our study was to letermine if interventional ventriculography could provide useful predictive data oncerning changes in left ventricular wall notion after successful thrombolytic coroary reperfusion. Analyzing both collateral low and PESP allowed us to identify 76% of egments that had improved regional wall notion after successful, sustained reperfuion. Force et al are correct in pointing out hat we have not conclusively demonstrated that the mechanism for chronic improvement in these segments is related to salvage of ischemic myocardium. This can only be accomplished by evaluating reperfusion in this subgroup of patients in a prospective randomized study.

Regional wall motion was determined using an area ejection fraction to overcome the poor reproducibility of other quantitative programs.[1] Sheehan et al[2] confirmed our findings using a centerline method of regional wall motion analysis.[3] They have further confirmed that compensatory hyperkinesia decreases in the nonischemic segments in the postextrasystolic beat.[2]

Experimental studies provide conflicting data concerning the presence of PESP in ischemic myocardium. Boden et al[4] and Sakamaki et al[5] demonstrated PESP to be maintained in ischemic myocardium up to 4 hours after coronary occlusion. Crozatier et al[6] and Force et al[7] conversely suggest that PESP is abolished within 5 minutes of coronary occlusion. These discrepancies may be explained by the methods used to measure wall motion. Strain gauges and 2-dimensional echocardiographic measurements, reflecting subepicardial and transmural wall motion, demonstrate that PESP is maintained. Ultrasonic crystals that reflect subendocardial wall motion demonstrate the loss of PESP early after occlusion. These findings suggest to us that the central, maximally ischemic zone rapidly loses inotropic reserve and rapidly undergoes myocardial necrosis. Myocardium with less severe ischemia, such as the subepicardium, has PESP maintained during prolonged ischemia.

Our findings suggest that interventional ventriculography accurately identifies marginally ischemic myocardial segments where thrombolytic reperfusion is most likely to result in myocardial salvage.

William W. O'Neill, MD
Ann Arbor, Michigan
28 February 1985

1. **Sheehan FH, Stewart DK, Dodge HT, Mitten S, Bolson EL, Brown BG.** Variability in the measurement of regional wall motion from contrast angiograms. Circulation 1983;68:550–559.
2. **Sheehan FH, Mathey DG, Dodge HT.** Postextrasystolic potentiation predicts recovery of LV function in patients reperfused late after infarction (abstr). JACC 1985;5:495.
3. **Bolson EL, Kliman S, Sheehan FH, Dodge HT.** Left ventricular segmental wall motion: a new method using local direction information. IEEE Comput Cardiol 1980;245–248.
4. **Boden WE, Liang C, Hood WB.** Postextrasystolic potentiation of regional mechanical performance during prolonged myocardial ischemia in the dog. Circulation 1980;61:1063–1070.
5. **Sakamaki T, Corday E, Meerbaum S, Torres MAR, Fishbein MC, Y-Rit J, Aosaki N.** Relation between myocardial injury and postextrasystolic potentiation of regional function measured by two-dimensional echocardiography. JACC 1983;2:52–62.
6. **Crozatier B, Franklin D, Theroux P, Tomoike H, Sasayoma S, Ross J.** Loss of regional postextrasystolic potentiation after coronary occlusion in dogs. Am J Physiol 1977;233:H392–H398.
7. **Force T, Kemper AJ, Cohen C, Parisi AF.** Early loss of postextrasystolic potentiation in acutely ischemic myocardium (abstr). Circulation 1984;70:II:II–183.

CORONARY ANGIOPLASTY IN MYOCARDIAL INFARCTION

The report by Papapietro et al[1] on percutaneous transluminal coronary angioplasty (PTCA) after administration of intracoronary streptokinase ignores the previous studies on this subject. To our knowledge, Meyer et al[2] first described the feasibility of PTCA in the setting of acute myocardial infarction (AMI) along with the clinical results in a group of 21 patients. This article was followed by a case report from our institution.[3]

Because reocclusion of the infarct-related vessel occurred in 4 of the 13 patients successfully dilated, Papapietro and associates[1] concluded that PTCA may not prevent rethrombosis. This is at variance with our finding[4]: The reocclusion rate demonstrated by angiography before discharge was reduced from 17% to 7% when PTCA was performed immediately after thrombolysis in the presence of a severe residual stenosis (58% diameter stenosis, as assessed from quantitative coronary angiography). This discrepancy can be explained by (1) the small numbers in both studies, and (2) the higher reocclusion rate after dilatation of a totally occluded vessel as in 2 of their cases.[5] Another major issue is the selection criteria for this procedure. Less severe underlying stenoses (50% diameter reduction) are not infrequent after thrombolysis (in one-third of the patients in our series[4]). By analogy with PTCA in stable angina, dilating mild lesions might expose the patients to the unnecessary risk of restenosis.[6] Furthermore, the incidence of restenosis and reinfarction are clearly related to the severity of the residual obstruction.[5,7] Thus, selection of the patients should be based on objective criteria rather than on visual evaluation of the angiograms. These and many other issues need to be addressed before the role of PTCA in the management of patients with AMI can be established.

William W. Wijns, MD
P. W. Serruys, MD
Rotterdam, The Netherlands
7 February 1985

1. **Papapietro SE, MacLean WAH, Stanley AWH, Hess RG, Corey DN, Arciniegas JG, Cooper TB.** Percutaneous transluminal coronary angioplasty after intracoronary streptokinase in evolving acute myocardial infarction. Am J Cardiol 1985;55:48–53.
2. **Meyer J, Merx W, Schmitz H, Erbel R, Kiesslich T, Dörr R, Lambertz H, Bethge C, Krebs W, Bardos P, Minale C, Messmer BJ, Effert S.** Percutaneous transluminal coronary angioplasty immediately after intracoronary streptolysis of transmural myocardial infarction. Circulation 1982;66:905–913.
3. **Meltzer RS, van den Brand M, Serruys PW, Fioretti P, Hugenholtz PG.** Sequential intracoronary streptokinase and transluminal angioplasty in unstable angina with evolving myocardial infarction. Am Heart J 1982;104:1109–1111.
4. **Serruys PW, Wijns W, van den Brand M, Ribeiro V, Fioretti P, Simoons ML, Kooijman CJ, Reiber JHC, Hugenholtz PG.** Is transluminal coronary angioplasty mandatory after successful thrombolysis? Br Heart J 1983;50:257–265.
5. **Heyndrickx GR, Serruys PW, van den Brand M, Vandormael M, Reiber JHC.** Transluminal angioplasty after mechanical recanalization in patients with chronic occlusion of coronary artery (abstr). Circulation 1982;66:suppl II:II–5.
6. **Ischinger T, Gruentzig AR, Hollman J, King III S, Douglas J, Meier B, Bradford J, Tankersley R.** Should coronary arteries with less than 60% diameter stenosis be treated by angioplasty? Circulation 1983;68:148–154.
7. **Harrison DG, Ferguson DW, Collins SM, Skorton DJ, Eriksen EE, Kioschos JM, Marcus ML, White CW.** Rethrombosis after reperfusion with streptokinase: importance of geometry of residual lesions. Circulation 1984;69:991–999.

MULTIPLE RISK FACTOR INTERVENTION TRIAL

The Multiple Risk Factor Intervention Trial Research Group presented a detailed and much needed further explication of their results, in particular the relation of baseline electrocardiographic abnormalities at rest and mortality.[1] Their results appear to show an excessive relative risk (1.67) for the special intervention (SI) group among those who had both an abnormal electrocardiogram at rest and systemic hypertension. In fact, as seen at the bottom of Table II, this is the only 1 of the 4 possible combinations of electrocardiograms and blood pressure at rest that was clearly against the SI group. (All nonhypertensive and hypertensive patients without baseline electrocardiographic abnormalities showed differences in the opposite direction). The investigators ascribed this mainly to sudden death within the first hour and invoked the presence of certain medications in the SI group. They further report that by Cox regression the difference between men with and without electrocardiographic abnormalities at rest is "nominally significant ($p = 0.02$)."

I wonder if the significant-appearing difference is clinically significant? After all, p values are merely indications of the strength of the evidence against the null hypothesis (no treatment difference) and cannot be considered as direct proof of a treatment effect. Moreover, a statistical evaluation for interaction in the 4 subgroups under consideration may or may not support the null hypothesis. As a non-statistician I would not wish to attempt this, but the authors may wish to examine that aspect.

David H. Spodick, MD, DSc
Boston, Massachusetts
18 February 1985

1. Multiple Risk Factor Intervention Trial Research Group. Baseline rest electrocardiographic abnormalities, antihypertensive treatment, and mortality in the Multiple Risk Factor Intervention Trial. Am J Cardiol 1985;55:1–15.

REPLY: We appreciate Spodick's comments. He has accurately summarized the main between-group (SI/Usual Care) findings we reported, and poses 2 further questions. To address first his second and more straightforward question: We had previously tested the 4-group interaction, and it does not reach conventional statistical significance ($p = 0.12$). Because this and a number of other analyses presented are not nominally significant, we would rephrase his other question as follows: If the adverse effect is real (e.g., not due to random error), is it of a magnitude to be clinically significant? We would be inclined to answer in the affirmative: A relative risk of 1.67 for coronary artery disease mortality or a relative risk of 2.34 for sudden death would be clinically significant. Whether the adverse effect is real is best answered by replication in other clinical trials. The available analyses from 2 previous trials show trends similar to the findings of the Multiple Risk Factor Intervention Trial for their coronary end points, but again, no definitive results.[1,2] Thus, for now, determination of the significance of these observations will have to rest on clinical judgment.

Jeffrey A. Cutler, MD, MPH
Bethesda, Maryland
James D. Neaton, PhD
Minneapolis, Minnesota
for the MRFIT Research Group
6 April 1985

1. Hypertension Detection and Follow-up Program Cooperative Group. Relationship between baseline ECG abnormalities and intervention on blood pressure. The HDFP experience. Circulation 1984;70:996–1003.
2. **Holme I, Helgeland A, Hjermann I, Leren P, Lund-Larsen PG.** Treatment of mild hypertension, with diuretics: the importance of ECG abnormalities in the Oslo Study and in MRFIT. JAMA 1984;251:1288–1299.

ASSESSMENT OF AMRINONE

I am pleased that Firth et al[1] completed their study comparing the inotropic and vasodilator effects of amrinone and isoproterenol. In May 1982, my co-workers and I studied the first patient of a group in whom we intended to compare these 2 agents. This and other trials of amrinone in our laboratory were cut short when the drug manufacturers unilaterally and without warning removed stocks of the drug held in our hospital on June 11, 1982. The removal of the drug by the pharmaceutical company occurred 1 week after I had presented at the Royal Society of Medicine preliminary data on the hemodynamic effects of intracoronary amrinone[2] and the effects of amrinone on isolated human myocardium and vessels.[3]

The study by Firth et al is yet another example in which investigators have failed to confirm that amrinone has positive inotropic effects.

According to the prescribing information on amrinone (Inocor®) supplied in the USA by its manufacturers (Winthrop-Breon), "amrinone lactate, represents a new class of cardiac inotropic agents ... indicated for the short term management of congestive heart failure." The data do not support many of the claims made by the manufacturers about this drug. In particular, the evidence does not support the view that amrinone is a positive inotropic agent in patients with congestive heart failure.

The drug may or may not be a positive inotropic agent in normal animals, animals with heart failure or humans without heart failure. This does not matter to the clinician. The drug may have effects on filling pressures and cardiac index in patients with heart failure as do all other vasodilators, and most are safer than amrinone. For the manufacturers to claim that a drug is an inotropic agent for use in patients with heart failure, they must show that it improves contractility in patients with heart failure, and drug-licensing authorities should be certain that they have adequately demonstrated the proof.

There are only 9 studies relevant to whether or not amrinone is a positive inotropic agent in patients with impaired left ventricular function.[1–9] Three studies[4–6] did demonstrate an increase in dP/dt max after the drug. However, these studies were small, did not seek to demonstrate a dose-response relation of altered contractility with serial doses of the drug and were biased toward finding an increase in contractility by virtue of their design as we have previously discussed.[7]

There have been 4 studies,[1,7–9] each with larger numbers of observations, in which a dose-response relation was sought. No evidence was found that amrinone improved many of indexes of contractility. Two studies compared amrinone with intravenous β-adrenergic agonists and found that amrinone produced no change in contractility, but dobutamine[8] and isoproterenol[1] produced dose-related increases. Another study compared amrinone with the pure vasodilator, nitroprusside, and found no significant difference.[9] In this study, increases in contractility after amrinone administration in a few patients were related to metabolic changes which suggested that they were the result of catecholamine release. Such catecholamine release commonly occurs with phosphodiesterase inhibitors like amrinone. Furthermore, amrinone does not alter the left ventricular end-systolic pressure-volume relation.[7]

Intracoronary infusions of amrinone[2] and a study that investigated the effect of amrinone on isolated human myocardium[3] do not suggest that amrinone has a positive inotropic effect in patients with cardiac failure.

It is therefore difficult to understand how amrinone has attained an undeserving reputation as an inotropic agent in patients with heart failure and why drug licensing authorities have been prepared to accept inadequate proof of efficacy.

Peter Wilmshurst, MRCP
London, UK
16 April 1985

1. **Firth BG, Ratner AV, Grassman ED, Winniford MD, Nicod P, Hillis LD.** Assessment of the inotropic and vasodilator effects of amrinone versus isoproterenol. Am J Cardiol 1984;54:1331–1336.
2. **Wilmshurst PT, Thompson DS, Dittrich HC, Dawson JR, Walker JM, Jenkins BS, Coltart DJ, Webb-Peploe MM.** Effects of intravenous and intracoronary amrinone in congestive cardiac failure (abstr). Circulation 1982;66:II:II–137.
3. **Wilmshurst PT, Walker JM, Fry CH, Mounsey JP, Twort CHC, Williams BT, Davies MJ, Webb-Peploe MM.** Inotropic and vasodilator effects of amrinone on isolated human tissue. Cardiovasc Res 1984; 18:302–309.
4. **Benotti JR, Grossman W, Braunwald E, Davolos DD, Alousi AA.** Hemodynamic assessment of amrinone: a new inotropic agent. N Engl J Med 1978; 299:1373–1377.
5. **Cárdenas LM, Vidaurri DA.** Estudio de los efectos hemodinámicos de diferentes dosis de un nuevo inótropico: La amrinona. Arch Inst Cardiol Mex 1979;49:961–968.
6. **Jennings K, Gwilt D, Crean P, Turnbull S, Gold R, Julian DG.** The clinical cardiovascular pharmacology of amrinone. A selective cardiotonic agent. Acta Cardiol (Brux) 1982;suppl 28:67–75.
7. **Wilmshurst PT, Thompson DS, Jenkins BS, Coltart DJ, Webb-Peploe MM.** Haemodynamic effects of intravenous amrinone in patients with impaired left ventricular function. Br Heart J 1983;49:77–82.
8. **Hermiller JB, Leithe ME, Magorien RD, Unverforth DV, Leier CV.** Amrinone in severe congestive heart failure: another look at an intriguing new cardioactive drug. J Pharmacol Exp Ther 1984;228:319–326.
9. **Wilmshurst PT, Thompson DS, Juul SM, Jenkins BS, Coltart DJ, Webb-Peploe M.** Comparison of the effects of amrinone and sodium nitroprusside on haemodynamics, contractility and myocardial metabolism in patients with cardiac failure due to coronary artery

disease and dilated cardiomyopathy. Br Heart J 1984;52:38–48.

EVALUATION OF CORONARY COLLATERAL CIRCULATION

A recent study by Elayda et al[1] discussed the relation between angiographic quality of coronary collateral circulation and preservation of left ventricular (LV) segmental wall motion. Analysis of LV regions supplied by 190 totally occluded arteries revealed no significant contractility differences between regions supplied by "good" collaterals and those supplied by "poor" collaterals. This conclusion differs substantially from that drawn by an article[2] of mine in 1974, which concluded that segmental LV wall motion was significantly better in those areas supplied by good collaterals. The reason for this difference is, I believe, that Elayda et al used inappropriate criteria in judging the adequacy of collateralization.

There is no doubt that it is difficult to angiographically gauge the quality of coronary collateral circulation. We lack a reliable quantitative method of accomplishing this, and therefore most such judgments end up being subjective. In my earlier study, I used the angiographic caliber of the distal segment of the occluded coronary artery as the primary criterion for determining adequacy of collateralization. This was based on the assumption that if the distal segment receives inadequate collateral flow, it will be underfilled and will therefore constrict. One can frequently observe the converse of this situation—that when normal flow is restored to such a vessel by coronary bypass, the distal segment dilates back up to its original caliber. Elayda et al instead used the degree of opacity of the distal segment as their sole criterion of collateral adequacy. In their study, collaterals were considered "good" if the opacity of the distal segment was 50% or more of the proximal segment, and "poor" if the opacity of the distal segment was less than 50% of the proximal segment. Of all the criteria one might choose to evaluate adequacy of collateralization, this seems to be the least reliable. The opacity of the distal segment of an obstructed coronary artery is directly related to the concentration of contrast material in the blood reaching that distal segment through collateral flow. If, as is frequently the case, a distal segment receives collateral flow from both the right and left coronary systems, its opacity will virtually always be reduced for the simple reason that coronary arteriography is performed by injecting only a single coronary artery at a time. For example, assume a patient with a dominant right coronary system has complete obstruction of the mid-right coronary artery, with well-developed collaterals supplying its distal segment from both the proximal portion of the right coronary artery and branches of the left anterior descending and circumflex arteries. During right coronary arteriography in such a case, the distal right coronary segment will appear poorly opacified because of inflow of unopacified blood from the branches of the left coronary system. On the other hand, when one performs a left coronary arteriogram in this patient, the distal right coronary artery will again appear poorly opacified because of inflow of unopacified blood from the proximal right coronary artery. Thus, although collateral circulation might be excellent in such a case, it would be classified as poor, using the criteria of Elayda et al, because of reduced opacity of the distal segment. There are other radiographic problems as well—variations in optical density of the cine film related to function of the automatic brightness control of the generator, presence or absence of soft tissue shadows caused by the diaphragm or patient habitus, etc. In view of this fallacious selection of criteria for assessing collateral quality, it is doubtful that their conclusion is justified. The authors cite a number of other supporting references; however, all of these were published before 1974 and many used similarly questionable methods of evaluation of collateral circulation.

Since publication of my article in 1974, other studies have been reported[3–7] which support the concept that collateral circulation does exert a protective role in preservation of LV myocardial viability and contractility. This does not imply, however, that collaterals can completely ameliorate the effects of myocardial ischemia or provide absolute protection against the development of myocardial infarction.

David C. Levin, MD
Boston, Massachusetts
1 March 1985

1. **Elayda MA, Mather VS, Hall RJ, Ali Massumi G, Garcia E, de Castro CM.** Collateral circulation in coronary artery disease. Am J Cardiol 1985;55:58–60.
2. **Levin DC.** Pathways and functional significance of the coronary collateral circulation. Circulation 1974;50:831–837.
3. **Hecht HS, Aroesty JM, Morkin E, Laraia PH, Paulin S.** Role of the coronary collateral circulation in the preservation of left ventricular function. Radiology 1975;114:305–313.
4. **Williams DO, Amsterdam EA, Miller RR, Mason DT.** Functional significance of coronary collateral vessels in patients with acute myocardial infarction: relation to pump performance, cardiogenic shock and survival. Am J Cardiol 1976;37:345–351.
5. **Schwarz F, Flameng W, Enssien R, Sesto M, Thormand J.** Effect of coronary collaterals on left ventricular function at rest and during stress. Am Heart J 1978;95:570–577.
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7. **Zimmern SH, Rogers WJ, Bream PR, Chaitman BR, Bourassa MG, Davis KA, Tyras DH, Berger R, Fisher L, Judkins MP, Mock MB, Killip TA.** Total occlusion of the left main coronary artery: The Coronary Artery Surgery Study (CASS) experience. Am J Cardiol 1982;49:2003–2010.

FREQUENCY OF PERICARDIAL EFFUSION BY M-MODE ECHOCARDIOGRAPHY AFTER ACUTE MYOCARDIAL INFARCTION

Kaplan et al[1] made a substantial contribution to the understanding of pericardial involvement during acute myocardial infarction. I have several questions including some points that they might wish to amplify to elucidate the message of their very worthwhile investigation. Although the text is carefully worded and I think no critical reader could make many misinterpretations, I wonder if pleuritic pain is enough of a criterion to decide that a patient has pericarditis. Like Kaplan et al, we frequently see such pain, but usually without a pericardial rub (which we use to confirm the diagnosis) and, of course, nearly always in the absence of a diagnostic electrocardiogram.[2] This report, in common with so many others, omits electrocardiographic changes and I assume that these were either rare or nonexistent. Indeed, there is no reason why this kind of pericarditis—limited to the infarct—should be associated with a typical ubiquitous ST-T elevation. Without a pericardial rub, therefore, pleuritic pain equally might represent pleuritis or pulmonary embolism, thus, the question arises: How many patients had signs of *pleural* effusion either on chest x-ray or in the echocardiogram? Kaplan et al themselves raise the question of epicardial fat being responsible for overdiagnosis of pericardial effusion and, of course, this could not be verified without a CT scan. Some smaller effusions could be due to congestive heart failure and one wonders about that datum among their patients. Their results with the distribution of pericardial rubs, site of infarction, and Q wave versus non-Q infarct are in accordance with ours.[2] On the other hand, there was an unusual predominance of female patients (10 of 16) among the patients with pericardial effusion, although the overall male dominance in pericarditis (27 of 16) was evident. Finally, of the small group that had pericardial rubs (8 of 43), how many were women?

These remarks are made to seek amplification rather than as direct criticism of a highly instructive, valuable investigation.

David H. Spodick, MD, DSc
Worcester, Massachusetts
4 March 1985

1. **Kaplan K, Davison R, Parker M, Przybylek J, Light A, Bresnahan D, Ribner H, Talano JV.** Frequency of pericardial effusion as determined by M-mode echocardiography in acute myocardial infarction. Am J Cardiol 1985;55:335–337.
2. **Krainin FM, Flessas AP, Spodick DH.** Infarction-associated pericarditis: rarity of diagnostic electrocardiogram. N Engl J Med 1984;311:1211–1214.

REPLY: Spodick's comments on our study are appreciated and raise a number of interesting questions. We agree that the cause of pleuritic chest pain after acute myocardial infarction (AMI) may be difficult to discern. In our diagnosis of clinical pericarditis, we included only patients with pleuritic pain that was clearly lessened by sitting up. None of our patients had pleural effusions, evidence of pulmonary emboli or chest wall tenderness. Likewise, no patient had electrocardiographic changes suggestive of pericarditis. Given the evanescent nature of pericardial friction rubs, in the setting of AMI we believe it is justifiable to diagnose clinical pericarditis by the presence of a classical symptom complex only. In our report 8 of the 12 patients with a diagnoses of pericarditis had rubs.

Our results suggest that the presence or absence of a pericardial effusion on M-mode echocardiography is not helpful in the differential diagnosis of pleuritic chest pain, probably because the pericarditis of myocardial infarction is a localized area of inflammation that may not be picked up by this limited technique and because there

may well be other causes for the presence of a pericardial effusion. For example, we agree with Spodick that some pericardial effusions after AMI may be a manifestation of congestive heart failure. This is indirectly supported by our finding that pericardial effusions are associated with a higher Killip classification and greater creatine phosphokinase release.

We share Spodick's interest in the greater frequency of pericardial effusions in females (10 of 16) vs males (6 of 27). This may reflect the finding of the Framingham study, that posterior extra echocardiographic spaces are present more often in women than in men.[1] We found a similar percentage of pericardial rubs in women (3 of 16) and men (5 of 27), but the numbers are too small to make conclusions with regard to differences in frequency between sexes.

Kerry Kaplan, MD
Richard Davison, MD
Chicago, Illinois
27 March 1985

1. **Savage DD, Garrison RJ, Brand F, Anderson SJ, Castelli WP, Kannel WB, Feinleib M.** Prevalence and correlates of posterior extra echocardiographic spaces in a free-living population based sample (The Framingham Study). Am J Cardiol 1983;51:1207–1212.

SUBCRITICAL CORONARY STENOSIS

The study by Brown et al[1] does not address a few points. Although the data are presented as if 2 groups of patients were being compared (the separating point being 20% coronary stenosis), 78 patients in the second group consisted of 74 persons with normal coronary arteries. These 74 therefore cannot be considered patients, and the numbers to be used for comparison should be 22 and 4, not 22 and 78. Even if the group of 74 persons comprised a subset of patients with heart disease *not* related to coronary stenosis and could still result in an abnormal thallium scan (which the authors do not elaborate on), they would still be comparing 2 different etiologic factors.

Currie et al[2] demonstrated that supine exercise is much more likely to result in a positive electrocardiographic stress test at a smaller workload than upright exercise; such a positive study revealed greater ST-segment deflections than the upright group. The study by Brown et al used both forms of exercise and used different end points (chest pain for upright and fatigue for supine exercise). With so many variables, they are not justified in reaching the conclusion that the 2 methods did not differ with regard to results.

Patients with "stress-induced" chest pain (as opposed to chest pain elicited on the treadmill) are described as having a higher incidence of abnormal thallium scans than those without. This contradicts their Methods section, which states that these were 100 consecutive patients who were studied because of chest pain. Were these patients' pain not related to exertion, was coronary spasm considered, and was ergonovine provocation study performed?

As an angiographer, I always maintain that visual "reading" of an angiogram may underestimate the physiologic significance of a lesion. However, I do not think that Brown et al proved that fact using their data.

Murthappa N. Prakash, MD
Bronx, New York
5 March 1985

1. **Brown KA, Osbakken M, Boucher CA, Strauss HW, Pohost GM, Okada RD.** Positive exercise thallium-201 test responses in patients with less than 50% maximal coronary stenosis: angiographic and clinical predictors. Am J Cardiol 1985;55:54–57.
2. **Currie PJ, Kelly MJ, Pitt A.** Comparison of supine and erect bicycle exercise electrocardiography in coronary heart disease: accentuation of exercise-induced ischemic ST depression by supine posture. Am J Cardiol 1983;52:1167–1173.

REPLY: Our study did not simply compare exercise thallium-201 imaging in 2 groups of patients with <50% coronary stenosis. The primary analysis of data used stepwise logistic regression which examined multiple patient variables. This analysis demonstrated that percent maximal angiographic stenosis, as a continuum, was a significant determinant of a positive thallium study. When patients were divided into 2 groups, somewhat arbitrarily by their maximal narrowing, we found that those with >20% maximal stenosis had a higher incidence of positive thallium tests than those with ≤20%. Our observation that thallium defects corresponded to the myocardial territory supplied by the coronary artery with <50% stenosis supports our contention that such apparently minor angiographic disease may have true hemodynamic impact. We see no reason to separate further those with ≤20% stenosis from those with apparently entirely normal coronary arteries. In fact, resolution of qualitative angiography is probably inadequate to distinguish such groups reliably. All persons had presented for evalution of chest pain severe enough to warrant catheterization and can be considered "patients," and not necessarily representative of a normal population.

We agree that data exists suggesting that supine vs upright exercise may influence stress-induced electrocardiographic changes in patients with coronary artery disease. However, as indicated in Table I of our study, we found no difference in electrocardiographic ischemia, frequency of reaching 85% maximal predicted heart rate or several other important patient variables between supine vs upright stress. Furthermore, method of exercise was not a predictor of thallium defect when analyzed using logistic regression. Finally, the endpoint for both upright and supine exercise was fatigue. For all these reasons, we felt justified in pooling the data.

"Stress-induced chest pain," typical or atypical for angina pectoris, refers specifically to chest pain elicited during the treadmill or bicycle exercise. All patients were brought to medical attention because of previous complaints of chest pain.

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10 April 1985

COLD-INDUCED IMMERSION INJURY

Campbell and Jewitt[1] report a rare episode of frostbite in a 46-year-old woman during a cold pressor test—hand immersion to the wrist in 0-degree iced water for 4.5 minutes. From "first hand" experience, 4.5 minutes in 0-degrees water is a very painful stimulus. It is unclear why 4.5 minutes was the endpoint of the cold pressor test since physiologic endpoints were not specified. After performing over 100 cold pressor tests[2–4] (applying crushed ice to the hand and forearm or immersing the hand in iced water and terminating the test when mean arterial pressure increased at least 10 mm Hg, in all cases less than 3 minutes), our study teams have never observed local complications. Although cold pressor testing is not standardized, cardiologists should identify an endpoint, such as change in mean arterial pressure, to limit cold exposure and minimize patient discomfort.

We agree with the authors' speculation that β-adrenergic blockade may exaggerate cold pressor test responses.[2]

Morton J. Kern, MD
San Antonio, Texas
12 March 1985

1. **Campbell S, Jewitt D.** Cold-induced immersion injury: a potential hazard of the cold pressor test. Am J Cardiol 1985;55:585–586.
2. **Kern M, Ganz P, Horowitz J, Mudge GH, Grossman W.** Potentiation of coronary vasoconstriction by beta-adrenergic blockade in patients with coronary artery disease. Circulation 1983;67:1178–1185.
3. **Kern MJ, Horowitz JD, Ganz P, Gasper J, Calucci WS, Lorell BH, Berry WH, Mudge GH Jr.** Attentuation of coronary vascular resistance by selective alpha-1 adrenergic blockade in patients with coronary artery disease. JACC 1985;5:840–846.
4. **Kern MJ, Petru MA, Ferry DR, Ellen DS, Barr WK, Porter CB, O'Rourke RA.** Regional coronary vasoconstriction after combined beta-adrenergic and calcium channel blockade in patients with coronary artery disease. JACC 1985;5:1438–1450.

CORONARY ARTERY OCCLUSION SEVEN WEEKS AFTER ANGIOPLASTY SUCCESSFULLY MANAGED WITH REPEAT EMERGENCY ANGIOPLASTY

We read with interest the study of Materne et al.[1] We wish to report our own experience which further illustrates the unstable nature of an occluded artery treated with angioplasty, and its successful management.

A 52-year-old woman underwent elective coronary angiography for angina pectoris. A 60% midright coronary artery (RCA) stenosis diameter reduction was followed by a 99% stenosis (Fig. 1A). Percutaneous transluminal coronary angioplasty (PTCA) was electively scheduled for the next morning. Earlier PTCA intervention, however, became mandatory with the onset of severe chest pressure and acute inferior ST-segment elevation. This was 7 hours after initial elective angiography. A totally occluded mid-RCA (Fig. 1B) was dilated (Fig. 1C), leaving a 10% stenosis at the site of earlier occlusion, and the more proximal 60% stenosis noted above. Total CK peaked at 107 IU/liter. The patient was discharged taking aspirin, dipyridamole and nifedipine.

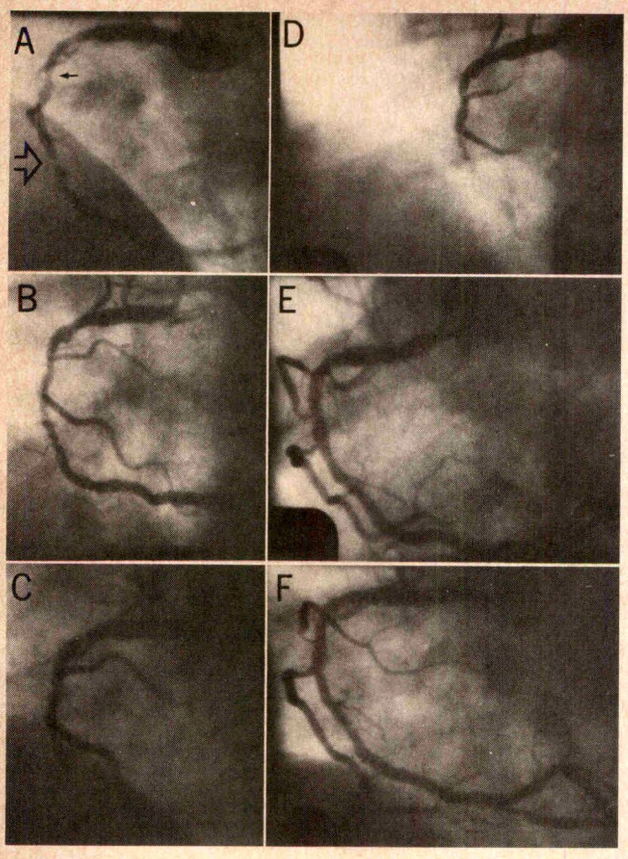

FIGURE 1. A, initial diagnostic angiogram of right coronary artery (left anterior oblique view) showing 60% stenosis (**small arrow**) and 99% stenosis (**large arrow**). **B,** right coronary angiogram (left anterior oblique view) showing acute occlusion of right coronary artery on evening of first hospital day. **C,** right coronary angiogram (left anterior oblique view) immediately after initial emergency percutaneous transluminal coronary angioplasty. **D,** 2 weeks. Right coronary angiogram (left anterior oblique view) after angioplasty of more proximal 60% stenosis. **E,** 7 weeks. Right coronary angiogram (left anterior oblique view) showing complete coronary occlusion at time of restudy. **F,** right coronary angiogram (left anterior oblique view) immediately after repeat emergency percutaneous transluminal coronary angioplasty.

Two weeks later, the patient was readmitted with recurrent angina at rest. Repeat angiography was unchanged in comparison to the post-angioplasty injections. Admission symptoms prompted angioplasty on the proximal 60% stenosis. This was reduced to a 10% stenosis, and the earlier angioplasty site remained widely patent (Fig. 1D). Previous medications were continued and the patient was discharged in satisfactory condition.

Seven weeks after the initial presentation, the patient was seen in the emergency room for acute, severe chest pressure, again associated with inferior ST-segment elevation. Angiography was repeated, and demonstrated total RCA obstruction at the site of the initial angioplasty (Fig. 1E). A 10% narrowing also was present at the more proximal PTCA site. Angioplasty was successfully repeated at the obstruction (Fig. 1F), and the total duration of chest pain was 2 hours. Intracoronary streptokinase (25,000 U) was administered to deter recurrent RCA thrombosis. The peak CK was 266 IU/liter. Radionuclide ventriculography at rest was performed 2 days later. The left ventricular ejection fraction was 61% and there were no regional wall motion abnormalities. Platelet aggregation studies and antithrombin III levels were normal. The patient continued to receive full-dose heparin therapy, and later therapy was converted to oral warfarin. Other discharge medications included dipyridamole and high-dose nifedipine.

This patient demonstrates that repeat coronary angioplasty may be successfully used for acute recurrent coronary arterial occlusion. Interim angiography confirmed arterial patency, and also in Materne's patient. Nonetheless, this was not predictive of a long-term satisfactory course.

Daniel I. Woronow, MD
Bruce W. Zinsmeister, MD
Joseph Lindsay, Jr., MD
Washington, D.C.
14 March 1985

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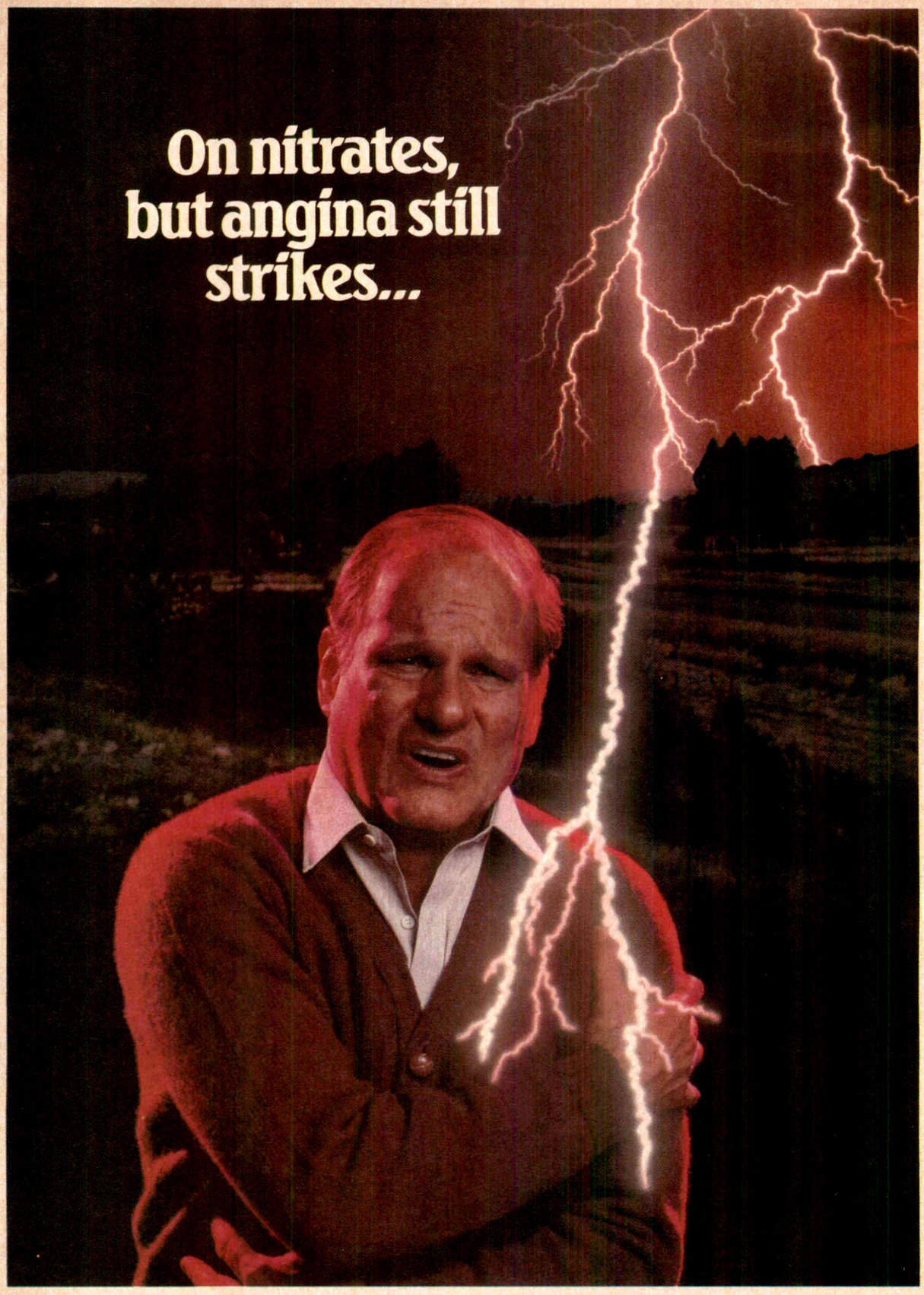
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Cardiovascular contraindications to the use of Isoptin are similar to those of beta blockers: severe left ventricular dysfunction, hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no artificial pacemaker is present) and second- or third-degree AV block.

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Please see brief summary on following page.

ISOPTIN®
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80 mg and 120 mg scored, film-coated tablets

Contraindications: Severe left ventricular dysfunction (see *Warnings),* hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction < 30% or moderate to severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. (See *Precautions.)* Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before ISOPTIN is used. (Note interactions with digoxin under *Precautions.*) ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild and controlled by decrease in ISOPTIN dose). Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations may disappear even with continued treatment; however, four cases of hepatocellular injury by verapamil have been proven by rechallenge. Periodic monitoring of liver function is prudent during verapamil therapy. Patients with atrial flutter or fibrillation and an accessory AV pathway (e.g. W-P-W or L-G-L syndromes) may develop increased antegrade conduction across the aberrant pathway bypassing the AV node, producing a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion, which has been used safely and effectively after ISOPTIN. Because of verapamil's effect on AV conduction and the SA node, 1° AV block and transient bradycardia may occur. High grade block, however, has been infrequently observed. Marked 1° or progressive 2° or 3° AV block requires a dosage reduction or, rarely, discontinuation and institution of appropriate therapy depending upon the clinical situation. Patients with hypertrophic cardiomyopathy (IHSS) received verapamil in doses up to 720 mg/day. It must be appreciated that this group of patients had a serious disease with a high mortality rate and that most were refractory or intolerant to propranolol. A variety of serious adverse effects were seen in this group of patients including sinus bradycardia, 2° AV block, sinus arrest, pulmonary edema and/or severe hypotension. Most adverse effects responded well to dose reduction and only rarely was verapamil discontinued. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patients should be carefully monitored to avoid over- or under-digitalization. ISOPTIN may have an additive effect on lowering blood pressure in patients receiving oral antihypertensive agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Clinical experience with the concomitant use of ISOPTIN and short- and long-acting nitrates suggest beneficial interaction without undesirable drug interactions. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C*: There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR < 50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%), elevations of liver enzymes have been reported. (See *Warnings.*) The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: ecchymosis, bruising, gynecomastia, psychotic symptoms, confusion, paresthesia, insomnia, somnolence, equilibrium disorder, blurred vision, syncope, muscle cramp, shakiness, claudication, hair loss, macules, spotty menstruation. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in round, scored, film-coated tablets containing either 80 mg or 120 mg of verapamil hydrochloride and embossed with "ISOPTIN 80" or "ISOPTIN 120" on one side and with "KNOLL" on the reverse side. Revised August, 1984. 2385

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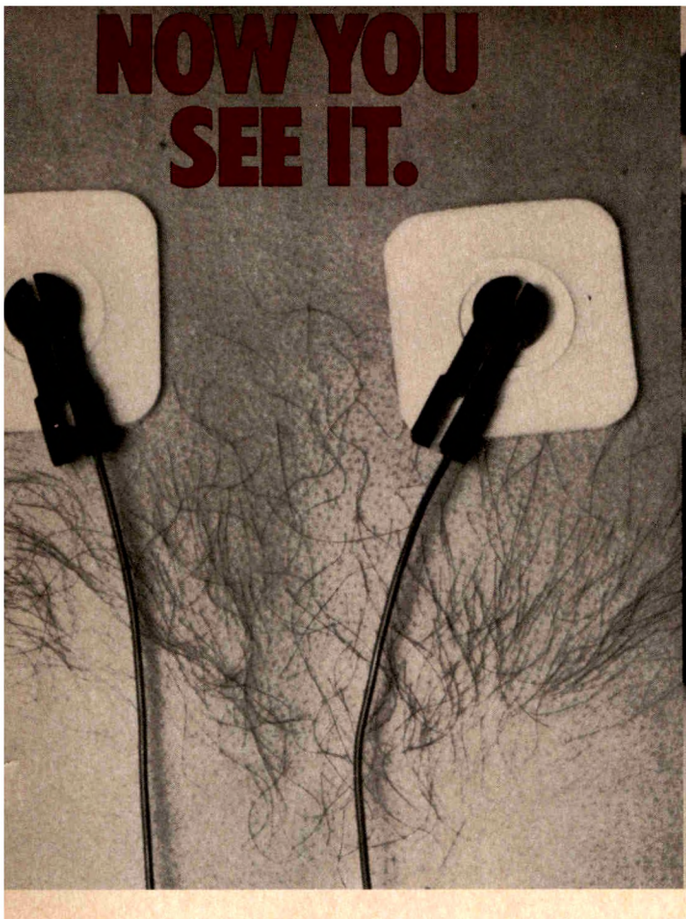

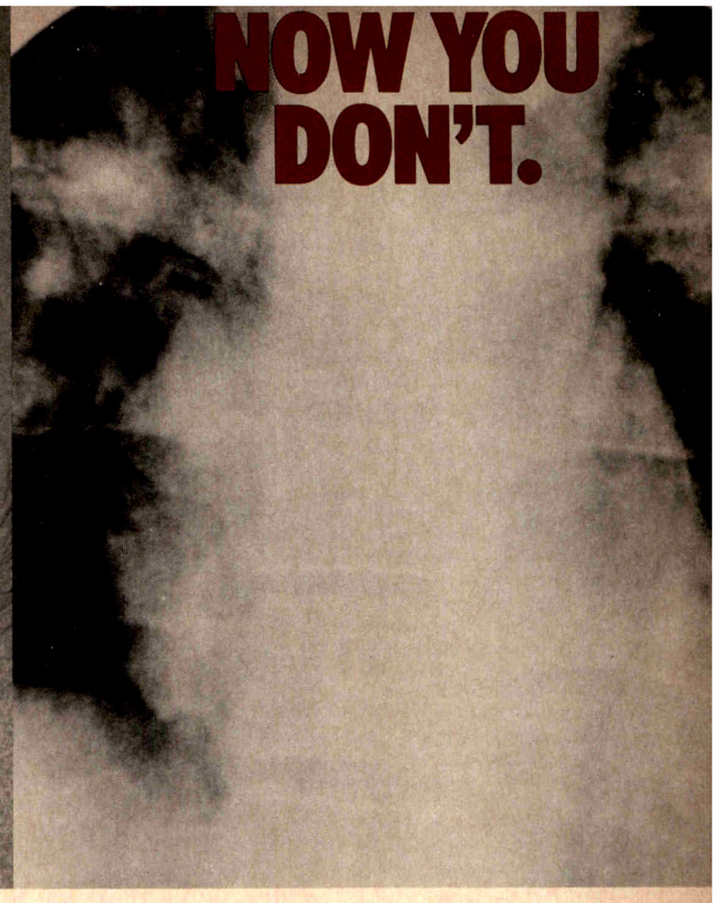

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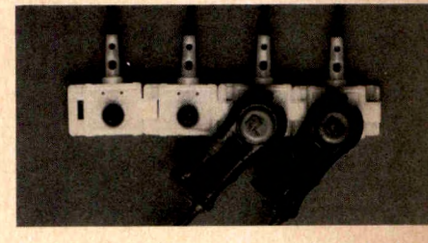

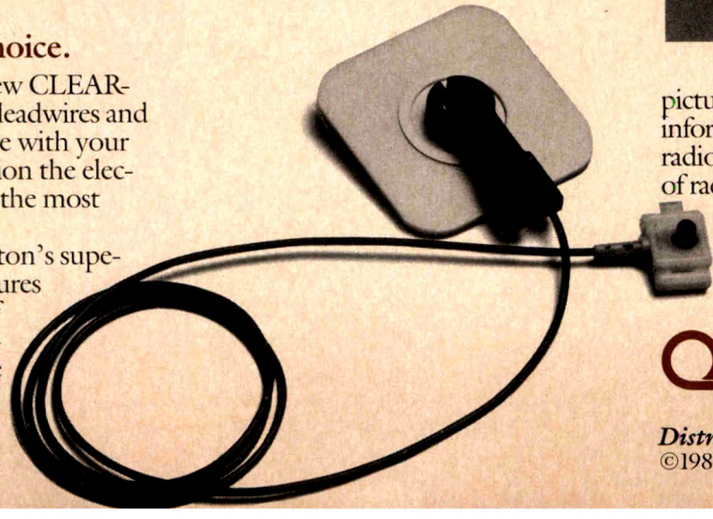

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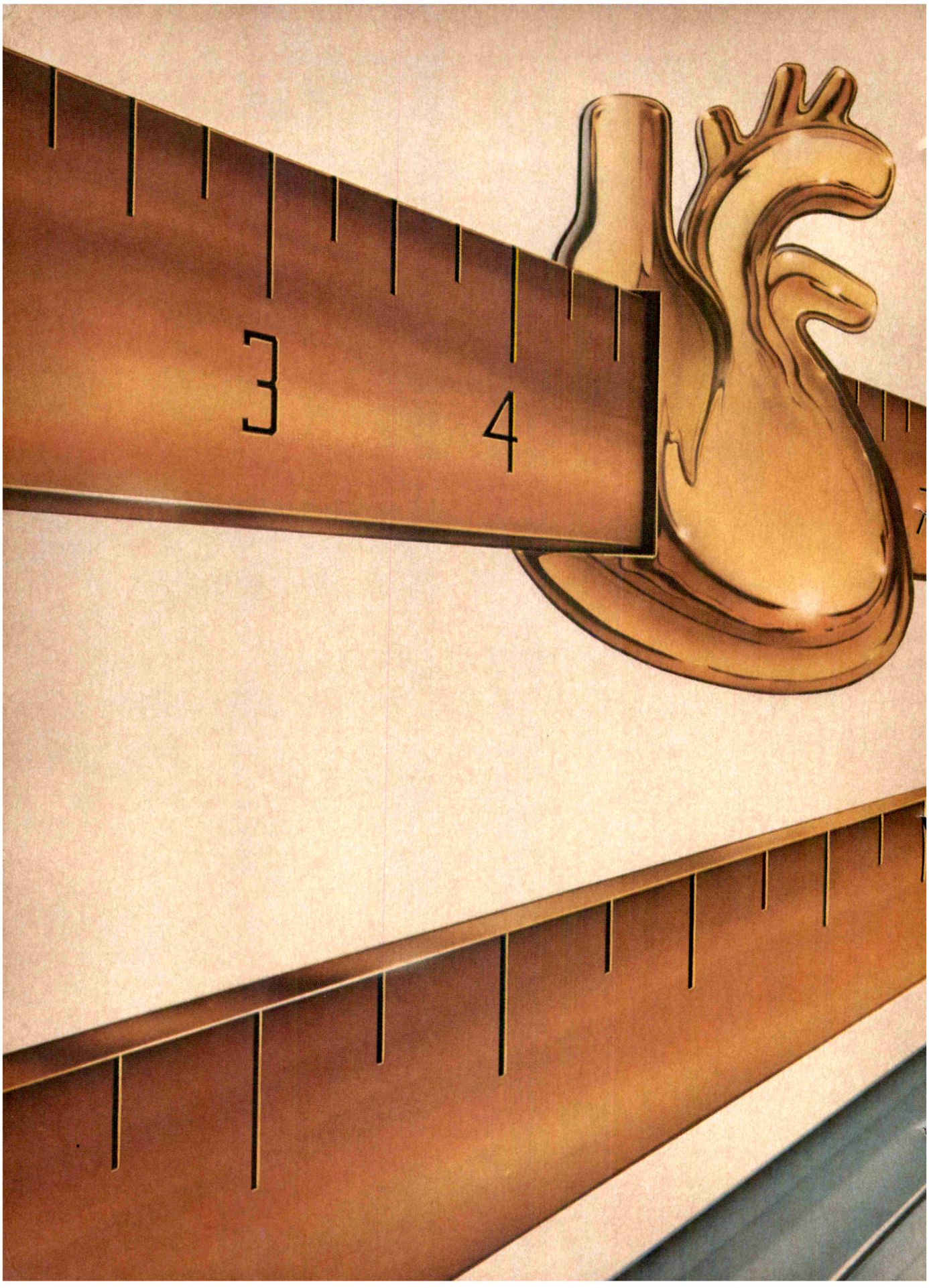
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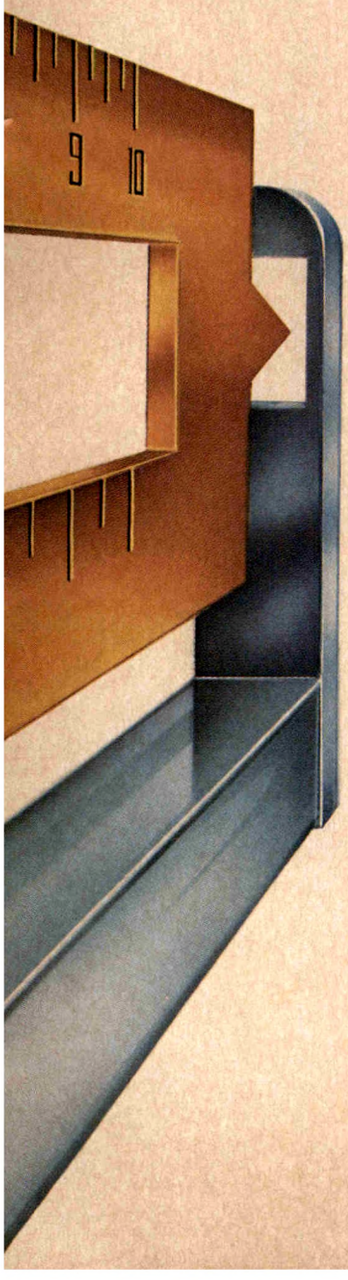

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Please see following page for reference and brief summary of full prescribing information.

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Reference: 1. National survey of 2,960 physicians, including 1,502 cardiologists and other physicians subspecializing in cardiology, conducted by Hoechst-Roussel Pharmaceuticals Incorporated, Somerville, New Jersey, August 1982.

Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide) Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.
There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

PREGNANCY: Pregnancy Category C. Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Furosemide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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BRIEF SUMMARY

INDICATIONS—Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indication as follows:
"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency of, or eliminate, anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack. Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.
PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.
ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.
DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25, 50 and 75 mg. For complete details, please see the full prescribing information.

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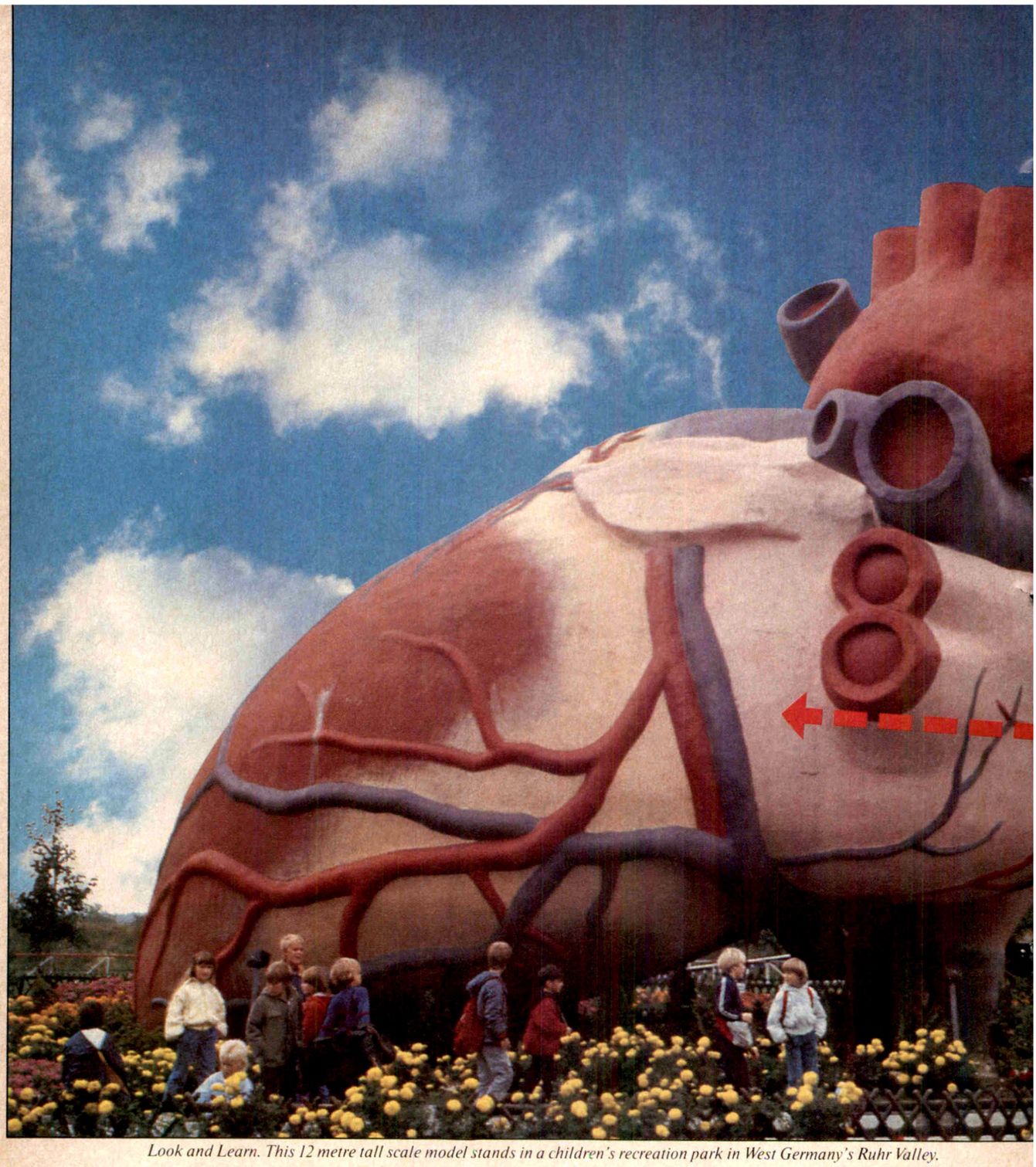

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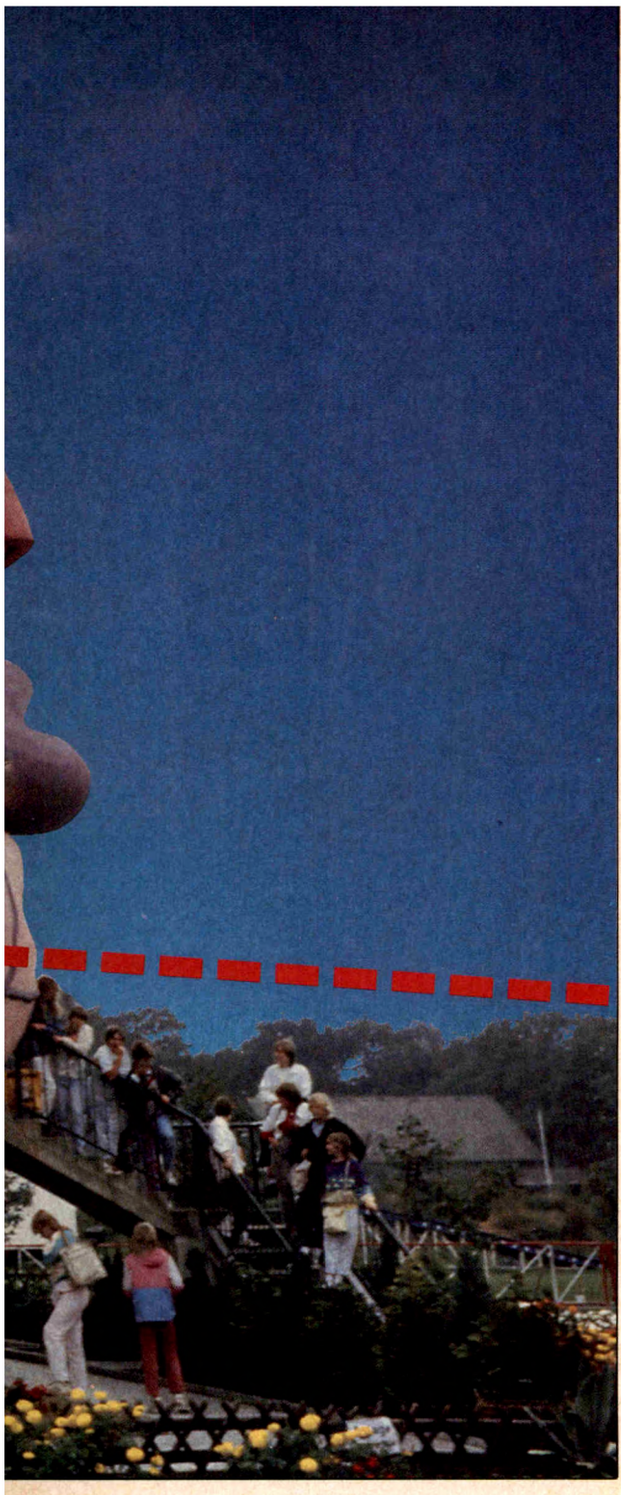

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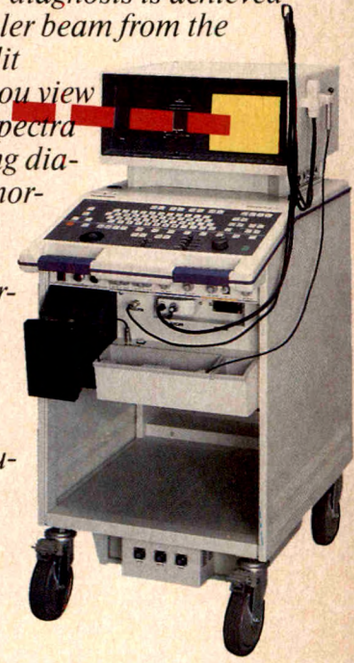

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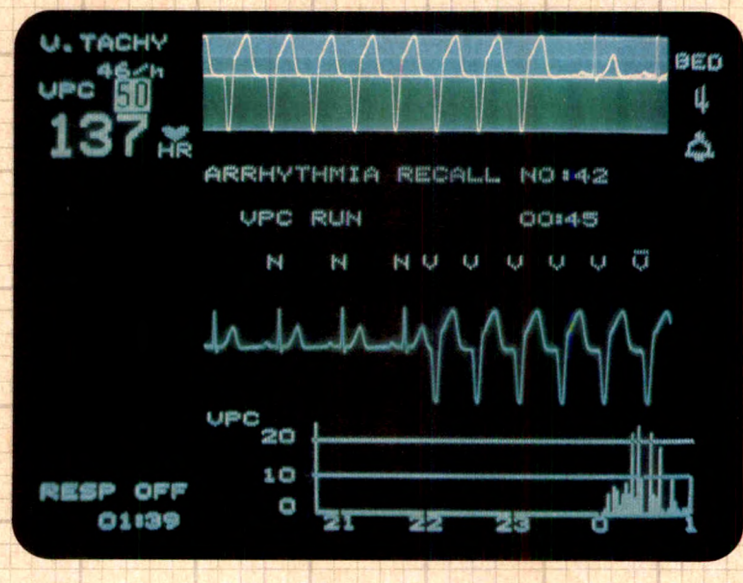

Like other antiarrhythmics, tocainide has not been shown to prevent sudden death, and also, like other antiarrhythmics, it has potentially serious adverse effects including the ability to worsen arrhythmias. Clinical and electrocardiographic evaluation should be used to periodically assess the need for therapy.

TONOCARD® (Tocainide HCl, MSD) is contraindicated in patients who are hypersensitive to this product or to local anesthetics of the amide type and in patients with second- or third-degree atrioventricular block in the absence of an artificial ventricular pacemaker.

Agranulocytosis, bone marrow depression, leukopenia, hypoplastic anemia, and thrombocytopenia have been reported in patients receiving TONOCARD; fatalities have occurred. Blood counts are recommended within the first two to three weeks of therapy and periodically thereafter. See Prescribing Information for details.

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

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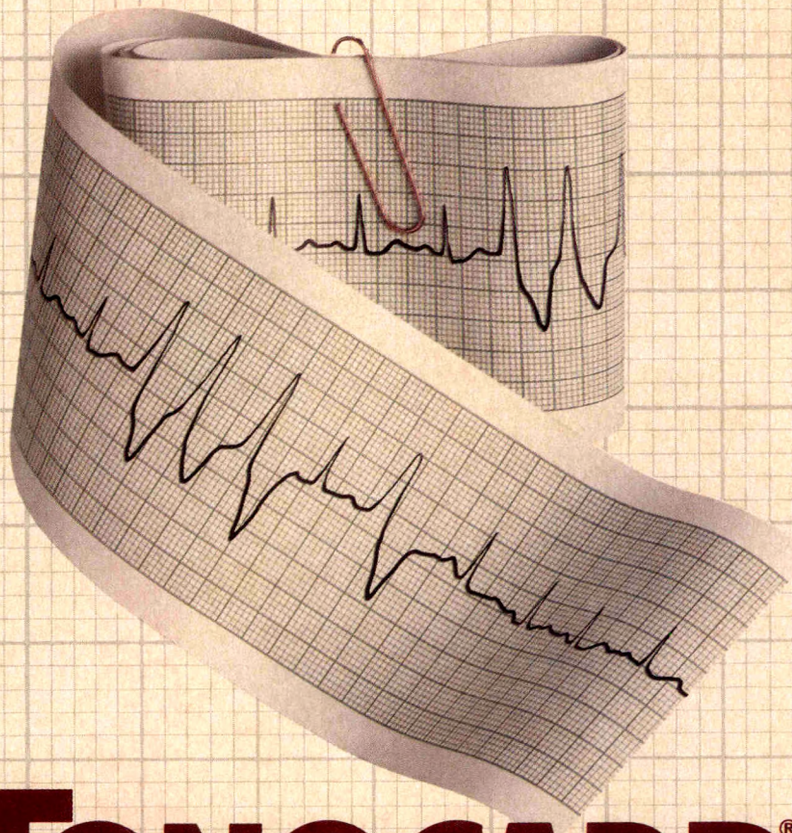

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CONTRAINDICATIONS

Patients who are hypersensitive to this product or to local anesthetics of the amide type.

Patients with second or third degree atrioventricular block in the absence of an artificial ventricular pacemaker.

WARNINGS

Blood Dyscrasias: Agranulocytosis, bone marrow depression, leukopenia, hypoplastic anemia and thrombocytopenia have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill and who were receiving concomitant drugs; fatalities have occurred. Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that blood counts, including differential and platelet counts, be performed at least once within the first two to three weeks of therapy, and periodically thereafter, particularly within the first three months of therapy. Blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat, or stomatitis), bruising, or bleeding. If any of these hematologic disorders is identified, TONOCARD should be discontinued and appropriate treatment should be instituted if necessary. Blood counts usually return to normal within one month of discontinuation. Caution should be used in patients with preexisting marrow failure or cytopenia of any type. (See ADVERSE REACTIONS).

Acceleration of Ventricular Rate: Acceleration of ventricular rate occurs infrequently when antiarrhythmics are administered to patients with atrial flutter or fibrillation (see ADVERSE REACTIONS).

PRECAUTIONS

General

Pulmonary Fibrosis: Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill. The experiences are usually characterized by bilateral infiltrates on x-ray and are frequently associated with dyspnea and cough. Fever may or may not be present. Patients should be instructed to promptly report the development of any pulmonary symptoms such as exertional dyspnea, cough or wheezing. Chest x-rays are advisable at that time. If these pulmonary disorders develop, TONOCARD should be discontinued. (See ADVERSE REACTIONS).

In patients with known heart failure or minimal cardiac reserve, TONOCARD should be used with caution because of the potential for aggravating the degree of heart failure.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing depression of cardiac conductivity.

In patients with severe liver or kidney disease, the rate of drug elimination may be significantly decreased (see DOSAGE AND ADMINISTRATION).

Since antiarrhythmic drugs may be ineffective in patients with hypokalemia, the possibility of a potassium deficit should be explored and, if present, the deficit should be corrected.

Like all other oral antiarrhythmics, TONOCARD has been reported to increase arrhythmias in some patients (see ADVERSE REACTIONS).

Information for Patients

Patients should be instructed to promptly report the development of bruising or bleeding; any signs of infections such as fever, chills, sore throat, or soreness and ulcers in the mouth; or any pulmonary symptoms, such as exertional dyspnea, cough, or wheezing.

Laboratory Tests

As with other antiarrhythmics, abnormal liver function tests, particularly in the early stages of therapy, have been reported. Periodic monitoring of liver function should be considered. Hepatitis and jaundice have been reported in some patients.

Drug Interactions

Specific interaction studies with digoxin and metoprolol have been conducted, no clinically significant interaction was seen with digoxin, but tocainide and metaprolol had additive effects on wedge pressure and cardiac index. TONOCARD has also been used in open studies with digitalis, beta-blocking agents, other antiarrhythmic agents, anticoagulants, and diuretics, without evidence of clinically significant interactions. Nevertheless, caution should be exercised in the use of multiple drug therapy.

TONOCARD is equally effective in digitalized and non-digitalized patients. In 17 patients with refractory ventricular arrhythmias on concomitant therapy, serum digoxin levels (1.1 ± 0.4 ng/mL) remained in the expected normal range (0.5-2.5 ng/mL) during tocainide administration.

Pregnancy

Pregnancy Category C. In a teratogenicity study in rabbits, tocainide was administered orally at doses of 25, 50, and 100 mg/kg/day (about 1 to 4 times the usual human dose). No evidence of a drug-related teratogenic effect was noted; however, these doses were maternotoxic and produced a dose-related increase in abortions and stillbirths. In a teratogenicity study in rats, an oral dose of 300 mg/kg/day (about 12 times the usual human dose) showed no evidence of treatment-related fetal malformations, but maternotoxicity and an increase in fetal resorptions were noted. An oral dose of 30 mg/kg/day (about twice the usual human dose) did not produce any adverse effects.

In reproduction studies in rats at maternotoxic oral doses of 200 and 300 mg/kg/day (about 8 and 12 times the usual human dose, respectively), dystocia, and delayed parturition occurred which was accompanied by an increase in stillbirths and decreased survival in offspring during the first week postpartum. Growth and viability of surviving offspring were not affected for the remainder of the lactation period.

There are no adequate and well-controlled studies in pregnant women. TONOCARD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether tocainide is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from TONOCARD, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

TONOCARD commonly produces minor, transient, nervous system and gastrointestinal adverse reactions, but is otherwise generally well tolerated. TONOCARD has been evaluated in both short-term (n = 1,358) and long-term (n = 262) controlled studies as well as a compassionate use program. Dosages were lower in most of the controlled studies (1200 mg/day) and higher in the compassionate use program (1800 mg and more). In long-term (2-6 months) controlled studies, the most frequent adverse reactions were lightheadedness/dizziness (15.3 percent), nausea (14.5 percent), paresthesia/numbness (9.2 percent), and tremor (8.4 percent). These reactions were generally mild, transient, dose-related and reversible with a reduction in dosage, by taking the drug with food, or by therapy discontinuation. Tremor, when present, may be useful as a clinical indicator that the maximum dose is being approached. Adverse reactions leading to therapy discontinuation occurred in 21 percent of patients in long-term controlled trials and were usually related to the nervous system or gastrointestinal system.

Adverse reactions occurring in greater than one percent of patients from the short-term and long-term controlled studies appear in the following table:

	Percent of Patients Controlled Studies	
	Short-term (n = 1,358)	Long-term (n = 262)
NERVOUS SYSTEM		
Lightheadedness/dizziness/vertigo/giddiness	8.0	15.3
Paresthesia/numbness	3.5	9.2
Tremor/quivering/tremulousness	2.9	8.4
Confusion/disorientation/hallucinations	2.1	2.7
Altered mood/awareness	1.5	3.4
Restlessness/shakiness/nervousness	1.5	0.4
Blurred vision/visual disturbances	1.3	1.5
Discoordination/unsteadiness/walking disturbances	1.2	0.0
Anxiety	1.1	1.5
Tinnitus/hearing loss	0.4	1.5
Ataxia	0.2	3.0
Nystagmus	0.0	1.1
GASTROINTESTINAL SYSTEM		
Nausea	15.2	14.5
Vomiting	8.3	4.6
Anorexia	1.2	1.9
Diarrhea/loose stools	0.0	3.8
CARDIOVASCULAR SYSTEM		
Hypotension	3.4	2.7
Bradycardia	1.8	0.4
Palpitations	1.8	0.4
Chest Pain	1.6	0.4
Conduction disturbances	1.5	0.0
Left ventricular failure	1.4	0.0
OTHER		
Sweating/cold sweat/night sweats/clammy	5.1	2.3
Headache	2.1	4.6
Tiredness/drowsiness/fatigue/lethargy/lassitude/sleepiness	1.6	0.8
Hot/cold feelings	0.5	1.5
Rash/skin lesion	0.4	8.4

An additional group of about 2,000 patients has been treated in a program allowing for the use of TONOCARD under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy, and comparatively high doses of TONOCARD were used. Fifty-four percent of the patients continued in the program for one year or longer, and 12 percent were treated for longer than three years, with the longest duration of therapy being nine years. Adverse reactions leading to therapy discontinuation occurred in 12 percent of patients (usually central nervous system effects or rash). A tabulation of adverse reactions occurring in one percent or more of patients follows:

	Percent of Patients Compassionate Use (n = 1,927)
NERVOUS SYSTEM	
Lightheadedness/dizziness/vertigo/giddiness	25.3
Tremor/quivering/tremulousness	21.6
Restlessness/shakiness/nervousness	11.5
Confusion/disorientation/hallucinations	11.2
Altered mood/awareness	11.0
Ataxia	10.8
Blurred vision/visual disturbances	10.0
Paresthesia/numbness	9.2
Nystagmus	1.1
GASTROINTESTINAL SYSTEM	
Nausea	24.6
Anorexia	11.3
Vomiting	9.0
Diarrhea/loose stools	6.8
CARDIOVASCULAR SYSTEM	
Increased ventricular arrhythmias/PVCs	10.9
CHF/progression of CHF	4.0
Tachycardia	3.2
Hypotension	1.8
Conduction disturbances	1.3
Bradycardia	1.0
OTHER	
Rash/skin lesion	12.2
Sweating/cold sweat/night sweats/clammy	8.3
Arthritis/arthralgia	4.7
Myalgia	1.7
Lupus	1.6

Adverse reactions occurring in less than one percent of patients in either the controlled studies or the compassionate use program or since the drug was marketed are as follows:

Nervous System: Coma, convulsions/seizures, depression, psychosis, mental change, agitation, altered taste/smell, difficulty concentrating, diplopia, dysarthria, impaired memory, increased stuttering/slurred speech, insomia/sleeping disturbance, local anesthesia, nightmares, thirst, weakness, myasthenia gravis.

Gastrointestinal System: Abnormal liver function tests, hepatitis, jaundice, (see PRECAUTIONS); stomatitis; abdominal pain/discomfort; constipation; dysphagia; gastrointestinal symptoms (including dyspepsia).

Cardiovascular System: Ventricular fibrillation, extension of acute myocardial infarction, cardiogenic shock, angina, AV block, hypertension, increased QRS duration, pleurisy/pericarditis, prolonged QT interval, right bundle branch block, syncope, vasovagal episodes, cardiomegaly, sinus arrest.

Pulmonary System: Respiratory arrest, pulmonary edema, pulmonary embolism, pulmonary fibrosis, fibrosing alveolitis, interstitial pneumonitis, pneumonia, dyspnea.

Other: Hematologic disorder (agranulocytosis, bone marrow depression, hypoplastic anemia, anemia, leukopenia, thrombocytopenia), increased ANA, urinary retention, polyuria/increased diuresis, alopecia, cinchonism, claudication, cold extremities, dry mouth, earache, edema, fever, hiccups, itching, leg cramps, malaise, metallic/menthol taste, muscle twitching/spasm, neck pain, pain radiating from neck, pallor/flushed face, pressure on shoulder, yawning.

Agranulocytosis, bone marrow depression, leukopenia, hypoplastic anemia, and thrombocytopenia have been reported (0.18 percent) in patients receiving TONOCARD in controlled trials and the compassionate use program. Many of these events occurred in patients who were seriously ill or who were receiving concomitant drugs; fatalities have occurred. Most of these events have been noted during the first 12 weeks of therapy. (See WARNINGS).

Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. The incidence of pulmonary fibrosis (including interstitial pneumonitis and fibrosing alveolitis) was 0.11 percent in controlled trials and the compassionate use program. These events usually occurred in seriously ill patients. Symptoms of these pulmonary disorders and/or x-ray changes usually occurred following 3-18 weeks of therapy and two patients died. (See PRECAUTIONS).

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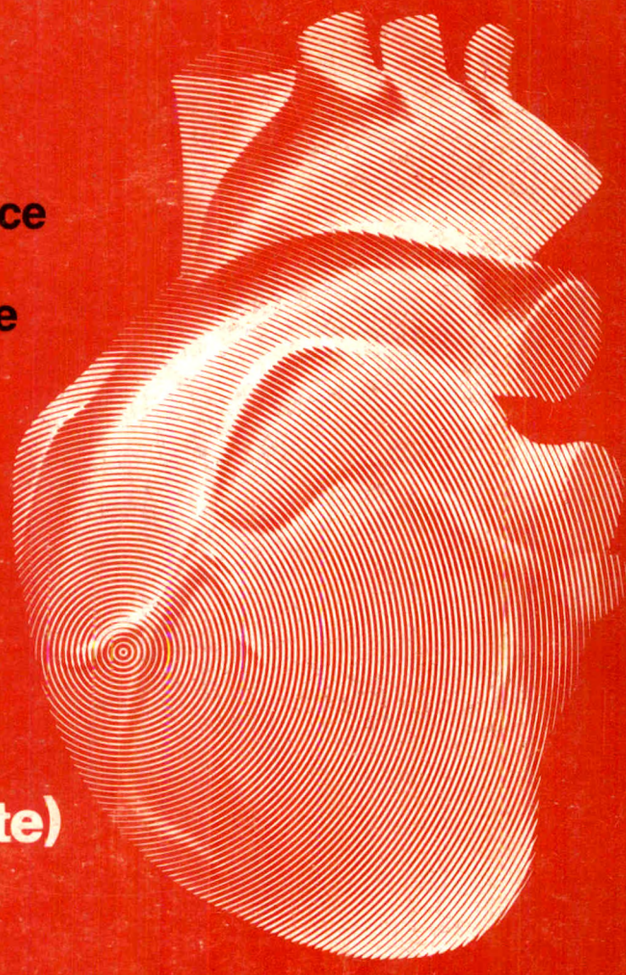

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With phenothiazines and reserpine	Additive cardiac depressive effects.
With hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine.
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PREGNANCY: The use of quinidine in pregnancy should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus. NURSING MOTHERS: The drug should be used with caution due to excretion of the quinidine in breast milk. ADVERSE REACTIONS: SYMPTOMS OF CINCHONISM (ringing in the ears, nausea, headaches, and/or disturbed vision) may appear in sensitive patients after a single dose of the drug. GASTROINTESTINAL: Diarrhea, nausea, vomiting, abdominal pain. CARDIOVASCULAR: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms (including ventricular tachycardia and fibrillation), paradoxical tachycardia, arterial embolism, and hypotension. HEMATOLOGIC: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis. CNS: Headache, fever, vertigo, apprehension, excitement, confusion, delirium, and syncope; disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis. DERMATOLOGIC: Rash, cutaneous flushing with intense pruritus, urticaria. HYPERSENSITIVITY REACTIONS: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity. See package insert for Full Prescribing Information.

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A Symposium:
Role of Calcium Entry–Blocking Drugs in Hypertension

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Edward D. Frohlich, MD

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A Symposium: Role of Calcium Entry–Blocking Drugs in Hypertension

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A Symposium: Role of Calcium Entry–Blocking Drugs in Hypertension

Introduction

EDWARD D. FROHLICH, MD

This 3-day symposium on "The Role of Calcium Entry–Blocking Drugs in Hypertension" brought together some of the leading investigators from around the world to discuss the latest advances in the field of hypertension therapy, including the applicability of calcium blockers.

The story of the calcium entry–blocking agents is remarkably similar to that of the β-blocking drugs. Although the first of the currently used β blockers appeared in 1964 (and it was even earlier for others), it was a long time before they were approved for the treatment of hypertension in the United States, some years after their approval for treatment of angina pectoris. In comparison, calcium antagonists were identified in 1962 as agents effective in treating acute hypertension. Their approval in the U.S. for angina followed 20 years later, and we are still awaiting approval for their use in hypertension.

The pioneer in delineating the properties of the calcium-channel blockers, Dr. Albrecht Fleckenstein, presented his recent work on the anticalcinotic (and antiarteriosclerotic) effects of calcium antagonists to begin the symposium. The effectiveness of calcium blockers as antihypertensive agents was the focus of several presentations. Dr. Fritz Buhler outlined the antihypertensive effects of these drugs, and pointed out that we have an additional calcium blocker—diltiazem—with which there is now considerable experience in the treatment of hypertension. As Dr. Barry Massie indicated, the calcium blockers verapamil, nifedipine and diltiazem are each comparable in efficacy to β blockers. Drs. Barry Materson and Marvin Moser and their colleagues showed that diltiazem was as effective as hydrochlorothiazide in treating hypertension in black patients. Drs. Robert O'Rourke and William Frishman cited studies showing that calcium antagonists are effective therapy for patients with hypertension and concomitant ischemic heart disease with angina pectoris.

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The role of the kidney in hypertension and in its treatment was another key topic discussed during the symposium. As Dr. Norman Hollenberg summarized, treatment strategies must take into account the renal response, because each class of antihypertensive drug has a different, and often limiting, effect on the kidney and vice versa.

The basic mechanism of action of the calcium blockers in hypertension—to dilate the blood vessels, thereby lowering blood pressure and reducing vascular resistance—is well understood. However, the discussions during this symposium have highlighted certain precautions. First, we must appreciate more clearly the cardiac effects of these agents—not only do they decrease vascular resistance, but they may also have a direct effect on the myocardium. Second, we must keep in mind the possible intracellular effect on protein synthesis by these agents as we learn the effect of these compounds in reducing cardiac mass. Third, we need greater sophistication in our understanding of

Edward D. Frohlich, MD

the intrarenal effects of the calcium-channel blockers. We still do not understand the mechanism of natriuresis—is it a hemodynamic effect, a redistribution of intrarenal flow or a result of selective cellular effects within the kidney? The concept of intrarenal flow distribution, as it relates to excretion of uric acid, sodium or even calcium may also be important.

Several interesting concepts have been introduced in this symposium that will undoubtedly be expanded upon in subsequent years. The prevention of calcinosis is intriguing, and its possible role in atherogenesis deserves further study. The relation of calcium blockers to spasm, especially cerebral vasospasm, was discussed by Drs. John and Rosemary Bevan. The interrelation of calcium and magnesium, and their effect on hormonal systems and on the intracellular effects of calcium, clearly need further definition. Finally, the possibility that certain concentrations of calcium either stimulate or inhibit protein synthesis was examined, along with the possible selective effect on the myocardium; both of these concepts merit further investigation.

The opportunity to exchange up-to-the-minute data in a field that is continuously changing is essential. The participants in this symposium certainly appreciated such an opportunity, and it is hoped that the reader will find the information compiled in this symposium supplement interesting and useful.

Experimental Basis of the Long-Term Therapy of Arterial Hypertension with Calcium Antagonists

ALBRECHT FLECKENSTEIN, MD, MARKUS FREY, MD, JÜRGEN ZORN, MD, and GISA FLECKENSTEIN-GRÜN, MD

In vascular smooth muscle (as in myocardial fibers) a transmembrane supply of Ca^{++} ions is required for active tension development. In consequence, Ca^{++} antagonists, which restrict transmembrane Ca^{++} delivery, possess a wide scope of action against practically all types of vasoconstrictor or spastic reactions on coronary, pulmonary, cerebral, renal or mesenteric arteries. Another important target of Ca^{++} antagonists is the resistance vessels of systemic circulation in both animals and humans. Thus, Ca^{++} antagonists are successfully used for the treatment of acute hypertensive crises as well as for long-term antihypertensive therapy.

Spontaneously hypertensive rats (SHRs) also respond to suitable Ca^{++} antagonists with a dramatic fall in blood pressure. The acute spasmolytic effects of Ca^{++} antagonists can be directly visualized by ophthalmoscopic examination of the arterioles in the ocular fundus. In untreated SHRs these arterioles are always heavily constricted, and aneurysm-like luminal protuberances develop. In contrast, after 1 adequate Ca^{++} antagonist dose, blood pressure instantaneously falls to its normal level while the retinal arterioles dilate.

A further important effect of Ca^{++} antagonists that we have demonstrated in experiments on SHRs is the prevention of progressive arterial Ca^{++} overload, which otherwise produces severe calcinotic or arteriosclerotic damage of the arterial walls. However, with the help of Ca^{++} antagonists, arterial integrity can be totally preserved. Interestingly, this anticalcinotic arterial protection by Ca^{++} antagonists may also manifest itself independent of any blood pressure change. This is true of arterial calcinosis in normotensive rats because of advanced age, alloxan diabetes or intoxication with overdoses of vitamin D_3, dihydrotachysterol or nicotine.

(Am J Cardiol 1985;56:3H–14H)

Excitation is a superficial process at the cell membrane, whereas contraction is an intracellular phenomenon. Therefore, there is a need for some kind of information transfer from the fiber surface to the internal contractile elements if the excitatory events are to be strictly linked with mechanical reactions. As is particularly obvious from observations on myocardial fibers and vascular smooth muscle cells, nature has solved this difficult problem with the help of Ca^{++} ions, which serve as messengers. During the past decade, definite evidence has been obtained in cardiac muscle of the existence of a special transmembrane carrier system for Ca^{++} ions, i.e., the so-called slow channels that open if the resting potential breaks down.

In consequence, a transmembrane influx of activator Ca^{++} sets in during cardiac excitation, together with a liberation of Ca^{++} from certain sarcoplasmic stores. The resulting increase in the intracellular concentration of free Ca^{++} ions initiates the splitting of adenosine triphosphate (ATP) by the Ca^{++}-dependent myofibrillar adenosine triphosphatase. In this way phosphate-bond energy is transformed into mechanical work. Various positive inotropic agents, e.g., adrenergic β-receptor stimulants, potentiate the transmembrane influx of Ca^{++} during cardiac excitation. In this way, they intensify both splitting of ATP and contractile force, while oxygen requirement for the subsequent ATP resynthesis increases. Conversely, every restriction of transmembrane Ca^{++} supply by simple extracellular Ca^{++} withdrawal, or by agents

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A comprehensive synopsis of these studies has recently been given by Fleckenstein.[1] The experimental studies were supported by grants from the Federal Ministry for Scientific Research and Technology, Bonn, Federal Republic of Germany.

that inhibit transmembrane Ca^{++} influx through the slow channels, reduces high-energy phosphate consumption and contractile tension development as well as oxygen demand.

In the early 1960s Fleckenstein studied several drugs that were able to modify the Ca^{++}-dependent contractile energy expenditure of the ventricular myocardium.[1–8] In the course of these investigations, the new pharmacologic family of "calcium antagonists" was found. These drugs block the slow-channel–mediated transmembrane Ca^{++} entry into the excited cardiac fibers in a highly specific way.[1,5,9] In addition, the existence of an analogous transmembrane carrier system for Ca^{++} ions was established in visceral and vascular smooth muscle. Interestingly enough, the sensitivity of the arterial vasculature to the inhibitory actions of the Ca^{++} antagonists proved to be even greater than that of the myocardium.[1,4,10–13]

Figure 1 shows the most important Ca^{++} antagonists identified by Fleckenstein and co-workers since 1964 on the basis of various electrophysiological, biophysical and biochemical tests.[1–7,9,14,16] Only diltiazem was added to this new pharmacologic family in 1975 by Japanese investigators.[15]

The Ca^{++} antagonists should be subdivided according to the profile of their actions on myocardial fibers into 2 groups. The first group, which we call group A, comprises the most potent and specific Ca^{++} antagonists such as verapamil, D 600 (the new generic name for D 600 is gallopamil), diltiazem, nifedipine and its derivatives niludipine, nimodipine, ryosidine and other 1,4-dihydropyridine compounds (Fig. 2). We have

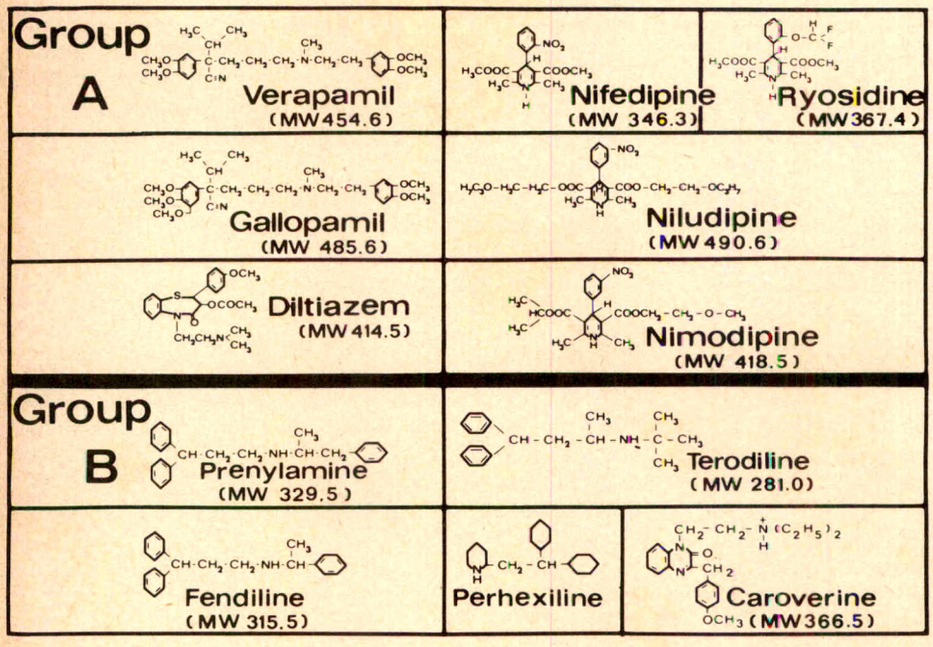

FIGURE 1. Specific calcium antagonists first identified in the Physiological Institute, Freiburg University (with the exception of diltiazem). For particular references see Fleckenstein.[1]

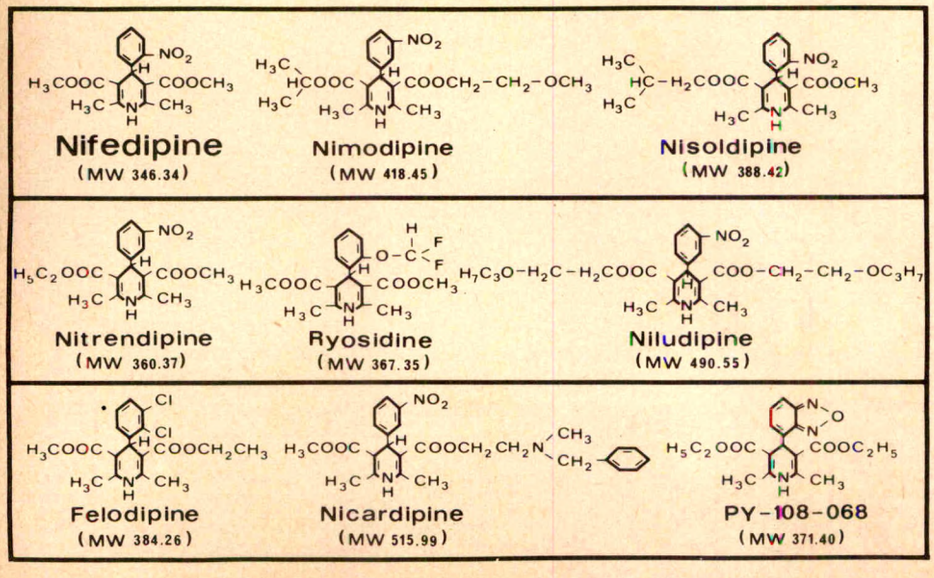

FIGURE 2. Highly specific 1,4-dihydropyridine calcium antagonists derived from the prototypical substance nifedipine. Nifedipine was identified in our laboratory as a top calcium antagonist in 1969/1970.[1–5,10,13,14,16] The code name was "Bay a 1040"; the usual trade name in Europe is "Adalat."

shown that the substances in group A are capable of inhibiting Ca^{++}-dependent excitation–contraction coupling of heart muscle by 95% and more, before the sodium and magnesium conductivities of the excited myocardial sarcolemma membrane are also affected.

Group B, on the other hand, includes prenylamine, terodiline, fendiline, perhexiline, caroverine and many other agents. The drugs of group B are somewhat less potent and less specific than those of group A, because they also inhibit the fast-channel–mediated sodium influx during the rising phase of action potential, if the inward Ca^{++} current has been lowered by 50 to 70%. In addition, the agents in group B are unable to discriminate between certain Ca^{++}- and magnesium-dependent bioelectric membrane effects; in contrast, the Ca^{++} antagonists in group A suppress the Ca^{++}-carried phenomena selectively.[1] Therefore, this discussion focuses on the Ca^{++} antagonists of group A, particularly verapamil, nifedipine and diltiazem. Moreover, this article deals preferentially with the manifestations of Ca^{++} antagonism on *vascular contractility*, which is certainly the most important target of Ca^{++} antagonists, at least with respect to the particular topic of this supplement.

In fact, the Ca^{++} antagonists of group A are the most efficient agents for suppression of vascular hyperactivity, which underlies excessive tone or spasms in various arteries of the coronary, pulmonary, cerebral, renal or intestinal circulation. Moreover, because these Ca^{++} antagonists strongly relax the systemic resistance vessels they also exhibit outstanding antihypertensive effects in both animals and humans.

Antihypertensive Effects of Calcium Antagonists

Significance of transmembrane calcium supply for activation of systemic resistance vessels: How do the Ca^{++}-antagonistic drugs interfere with contractile activation of vascular smooth muscle? Taking coronary smooth muscle as an example, Figure 3 shows that there are 2 physiologic sources of activator Ca^{++} for vasoconstriction. Probably the most important pathway (I) by which Ca^{++} is supplied for contractile activation consists of a potential or receptor-dependent Ca^{++} influx through plasma membrane channels, as shown in the upper half of Figure 3. Alternating electric square wave stimulation, depolarization with high extracellular potassium, quick stretch, cardiac glycosides and coronary vasoconstrictor agonists such as acetylcholine, serotonin and histamine, as well as noradrenaline (after previous β-receptor blockade), open these transmembrane Ca^{++} channels. The resulting contractile responses are of tonic character and are most responsive to the inhibitory action of Ca^{++} antagonists. The second alternative pathway (II) is shown in the lower half of Figure 3. Here Ca^{++} can be released from cellular storage sites by "receptor-operated" nonelectric mechanisms. The resulting contractile responses to this cellular Ca^{++} release are of phasic character. Ca^{++} withdrawal or Ca^{++} antagonists do not directly impair the Ca^{++} release from cellular depots, but inhibit (in a somewhat higher concentration) transmembrane replenishment of the Ca^{++} stores after Ca^{++} release.

In considering the 2 alternative pathways, it becomes obvious that the pattern of contractile activation of the systemic resistance vessels corresponds best with the transmembrane type (I) of Ca^{++} supply, which also predominates in the vasculature of the extramural coronary stem arteries. Thus, there is a striking similarity between the behavior of coronary smooth muscle and of the systemic resistance vessels.[1,10,12,13] For example:

1. Both extramural coronary wall tension and systemic flow resistance are highly responsive to changes in the extracellular Ca^{++} concentration. More precisely, if the transmembrane Ca^{++} supply from extracellular sources is interrupted by simple Ca^{++} withdrawal or by Ca^{++} antagonists, coronary

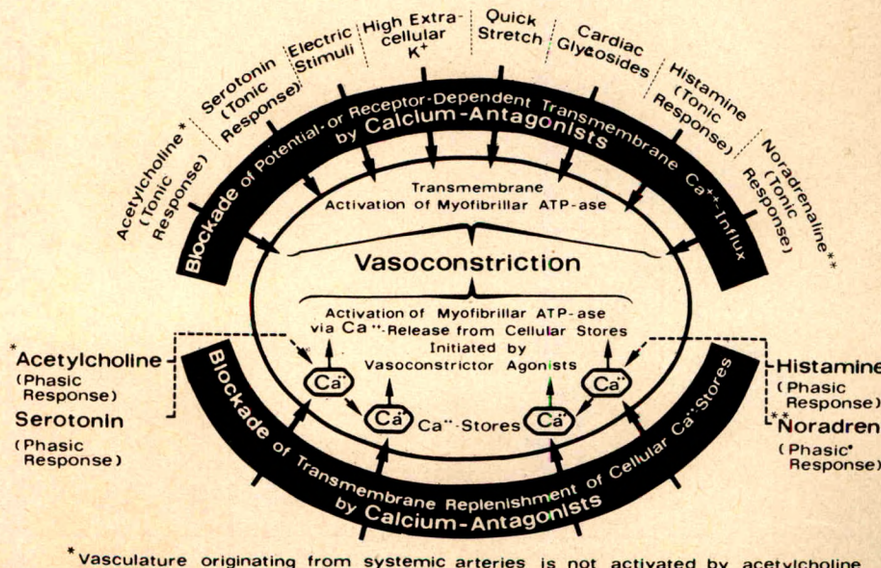

FIGURE 3. Scheme of the dual source of activator Ca^{++} for the tonic and phasic vascular smooth muscle contractions; i.e., (I) potential-or receptor-dependent transmembrane Ca^{++} supply for tonic responses, and (II) release of Ca^{++} from cellular stores for phasic responses to vasoconstrictor agonists. The Ca^{++} antagonists directly and most effectively inhibit transmembrane Ca^{++} influx, i.e., pathway I. However, to a lesser extent Ca^{++} antagonists also interfere with pathway II, probably indirectly by impairing transmembrane replenishment of cellular Ca^{++} stores. The exact anatomical location of these cellular Ca^{++} stores is a pending problem. Reprinted from Fleckenstein.[1]

*Vasculature originating from systemic arteries is not activated by acetylcholine

**Noradrenaline produces contraction of extramural coronary vasculature only after previous β-receptor blockade

tension development and systemic arteriolar tone break down.

2. In both coronary smooth muscle and systemic resistance vessels, there is a strong natural competition between Ca^{++} and hydrogen ions and a high sensitivity to any change in their ratio. Therefore, accumulation of hydrogen ions, in cases of local or general acidosis, always produces vasodilation by counteracting Ca^{++} ions. Conversely, alkalosis, by lowering the hydrogen ion concentration, potentiates the vasoconstrictor effects of Ca^{++} ions.[1,11,17,18] In all probability, hydrogen ions inhibit transmembrane Ca^{++} entry in coronary arteries and resistance vessels, and also interfere with the Ca^{++}-dependent internal activation of myofibrillar adenosine triphosphatase.

3. At a constant, normal pH, excessive Ca^{++}-dependent tone of the coronary vasculature and the systemic resistance vessels can best be lowered by the use of Ca^{++} antagonists. Interestingly enough, the Ca^{++} antagonists of group A with the strongest vasodilator effects on the coronary vasculature also reduce the flow resistance in systemic circulation with a similarly high efficacy.

Experimental evidence of therapeutic blood pressure control with calcium antagonists: The long series of clinical investigations on the antihypertensive effects of Ca^{++} antagonists began with verapamil even before the Ca^{++}-antagonistic mechanisms of action of this drug had been generally recognized. Apart from early experimental observations in our laboratory,[8] 4 clinical research groups directed by Heidland,[19] Brittinger et al,[20] Bender[21] and Belz[22] carried out the first therapeutic trials in different German clinics in the middle and late 1960s, independent of one another. They were particularly interested in the *acute* antihypertensive effects of verapamil. Brittinger and co-workers realized the usefulness of verapamil in the treatment of hypertensive crises.[20] Moreover, Japanese physicians in the early 1970s recognized the therapeutic value of verapamil in chronic hypertension as well and applied it for stroke prophylaxis.

A detailed analysis of the Ca^{++} dependency of coronary and systemic vascular resistance and its acute attenuation by the Ca^{++} antagonists verapamil, gallopamil and nifedipine was published in 1972 by Grün and Fleckenstein.[13] Subsequently, in order to visualize the antihypertensive effects of verapamil[23] and other Ca^{++} antagonists in long-term studies, we treated spontaneously hypertensive rats (SHRs) with daily oral doses for 4 to 18 months. The therapy was always started at the age of 1 month. As can be seen from the upper curve in Figure 4, hypertensive rats that were not given a Ca^{++} antagonist showed an increase of blood pressure of nearly 100% within 5 months, up to approximately 200 mm Hg. In contrast, hypertensive rats treated with verapamil behaved like normotensive control Wistar Kyoto rats (WKYs) of the same age—the blood pressure of the verapamil-treated rats (represented by the hatched curve) remained at the low level of 110 mm Hg. However, when the therapy was discontinued, arterial blood pressure rapidly rose within a day to the high level of untreated hypertensive rats.

Nifedipine and other Ca^{++}-antagonistic 1,4-dihydropyridine derivatives have also been shown in our studies to exert antihypertensive actions. This applies

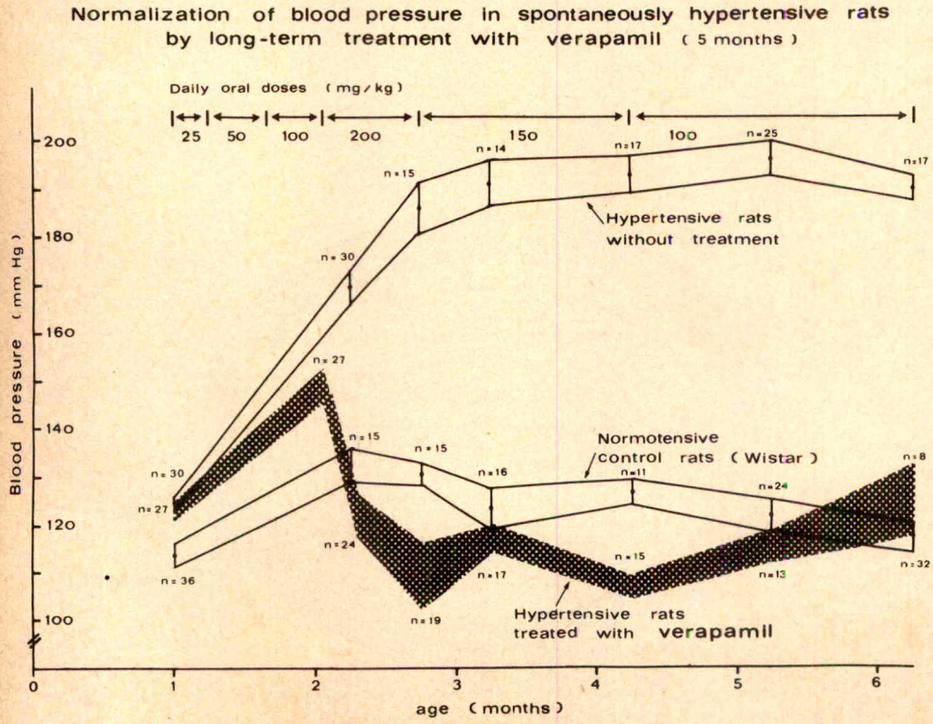

FIGURE 4. Normalization of mean arterial blood pressure of spontaneously hypertensive rats by chronic oral administration of verapamil for 5 months. Treatment lasted from the end of the first to the end of the sixth month of age. Data from von Witzleben et al.[23] (See Fleckenstein-Grün and Fleckenstein.[12])

for nifedipine, nimodipine, nisoldipine, nitrendipine, niludipine, ryosidine, felodipine and nicardipine. Diltiazem also belongs to this class of antihypertensive Ca^{++} antagonists. Figure 5 represents observations obtained from SHRs. Here, normalization of blood pressure was achieved by acute oral treatment with diltiazem, after hypertension of more than 200 mm Hg had been fully maintained for at least 14 months during a previous observation period of 19 months. This experiment shows a true therapeutic effect, in contrast to the antihypertensive prophylaxis in the foregoing studies.

In recent years, nifedipine and other Ca^{++} antagonists have also been shown to exert antihypertensive actions in other disease models. For instance, normalization of high blood pressure by chronic treatment with nifedipine was also observed in sodium-loaded, salt-sensitive Dahl rats.[24] Similarly, conscious renal-hypertensive dogs are rather responsive to Ca^{++} antagonists. As shown by Hiwatari and Taira,[25] an acute fall of blood pressure could be obtained in these animals with 1 oral dose of niludipine 1 to 3 mg/kg. Diltiazem also proved to be effective in the treatment of spontaneously hypertensive, renal-hypertensive and desoxycorticosterone/saline-loaded hypertensive rats.[26]

Parallel suppression of hypertension and arterial calcium overload with calcium antagonists: According to our observations with the Ca^{++} antagonists of group A, a strong antihypertensive action is common to all these agents. Differences in strength can usually be compensated for by adjusting the dose. Another effect shared by all antihypertensive Ca^{++} antagonists of group A is the prevention of excessive Ca^{++} accumulation in the arterial walls.[1,12,27–30] In untreated hypertensive rats, the Ca^{++} content of the arterial walls steadily rises until, at an age of 18 to 20 months, it may reach a value that is approximately 2 to 3 times as high as in normotensive control WKYs of the same age. However, using Ca^{++} antagonists, both blood pressure and arterial Ca^{++} content could be kept at normal levels seen in these long-term experiments. Figure 6 shows a series of observations on SHRs with or without prophylactic oral administration of nitrendipine. In fact, corresponding to the complete prevention of hypertension over an observation period of 18 months, there was also *no* abnormal increase in the Ca^{++} content of the aortic and mesenteric arterial walls. In none of these experiments with Ca^{++} antagonists of group A have we found any dissociation between their antihypertensive and their anticalcinotic actions.

Prevention of severe arteriolar constriction and arterial damage by long-term treatment of spontaneously hypertensive rats with calcium antagonists: In SHRs, which are generally regarded to resemble human patients with essential hypertension,

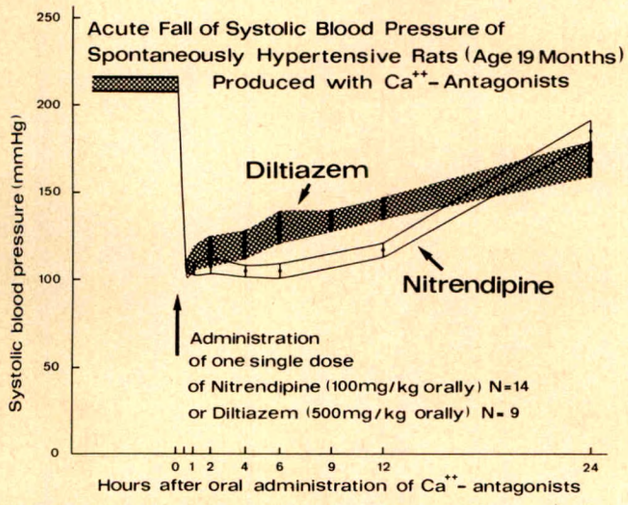

FIGURE 5. Instantaneous normalization of arterial blood pressure of 19-month-old spontaneously hypertensive rats after oral administration of 1 dose of nitrendipine (n = 14) or diltiazem (n = 9). Before administration of nitrendipine or diltiazem, the spontaneously hypertensive rats had maintained a blood pressure level >200 mm Hg for at least 14 months (see Fig. 6A, upper curve). In response to the Ca^{++} antagonists, the arteriolar spasm in the ocular fundus disappeared simultaneously with the acute fall in blood pressure, whereas the aneurysms persisted. Spontaneously hypertensive rats, at an age <12 months, tolerated the acute lowering of blood pressure without undesired adverse effects. Two heavily arteriosclerotic 19-month-old rats (out of 23) died within 24 hours after administration of the Ca^{++} antagonists.

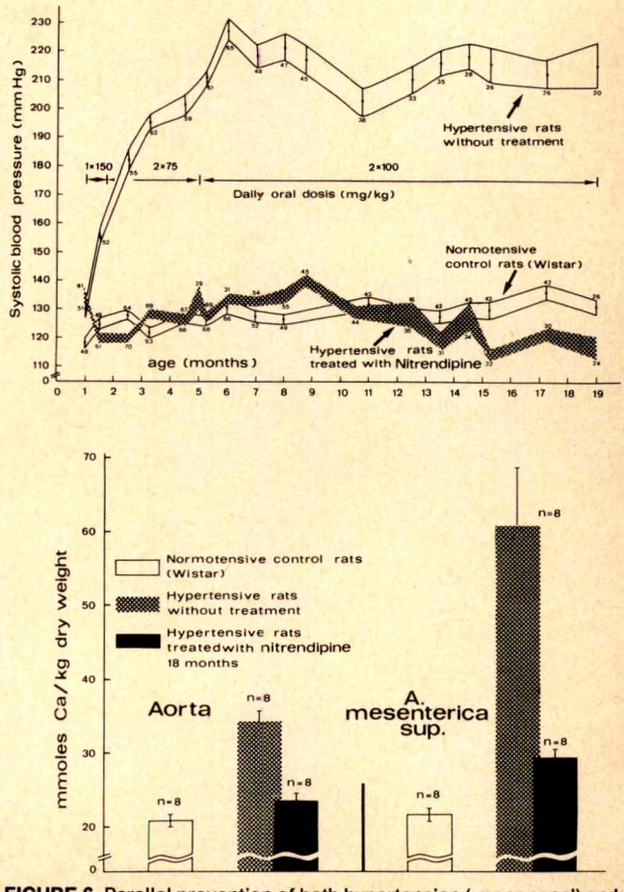

FIGURE 6. Parallel prevention of both hypertension (upper panel) and Ca^{++} overload of the aortic and mesenteric walls (bottom panel) by prophylactic oral treatment with nitrendipine over 18 months.

the increase in systemic arteriolar tone can be visualized directly by examination of the ocular fundus. As already known from observations by Takahashi,[31] the caliber of the retinal arterioles diminishes in SHRs during the period of progressive blood pressure elevation. In consequence, the ratio of the caliber of the retinal arterioles to that of the veins, which is normally around 1:2, changes considerably. In our studies, the arteriolar diameter in the state of fully developed hypertension was only about one-fourth of that of the accompanying retinal veins (Fig. 7A and B). However, apart from uniform spastic constriction, irregularities of the arteriolar diameter appear in the form of indentations, aneurysmal dilations or "rosary-like" alternations of extremely narrowed and expanded sections. There is a clear time-dependent progression of these luminal irregularities in that the ocular arterioles of 3-month-old hypertensive rats only exhibited a uniform constriction, whereas at a later stage, the occurrence of aneurysm-like protuberances became more frequent.

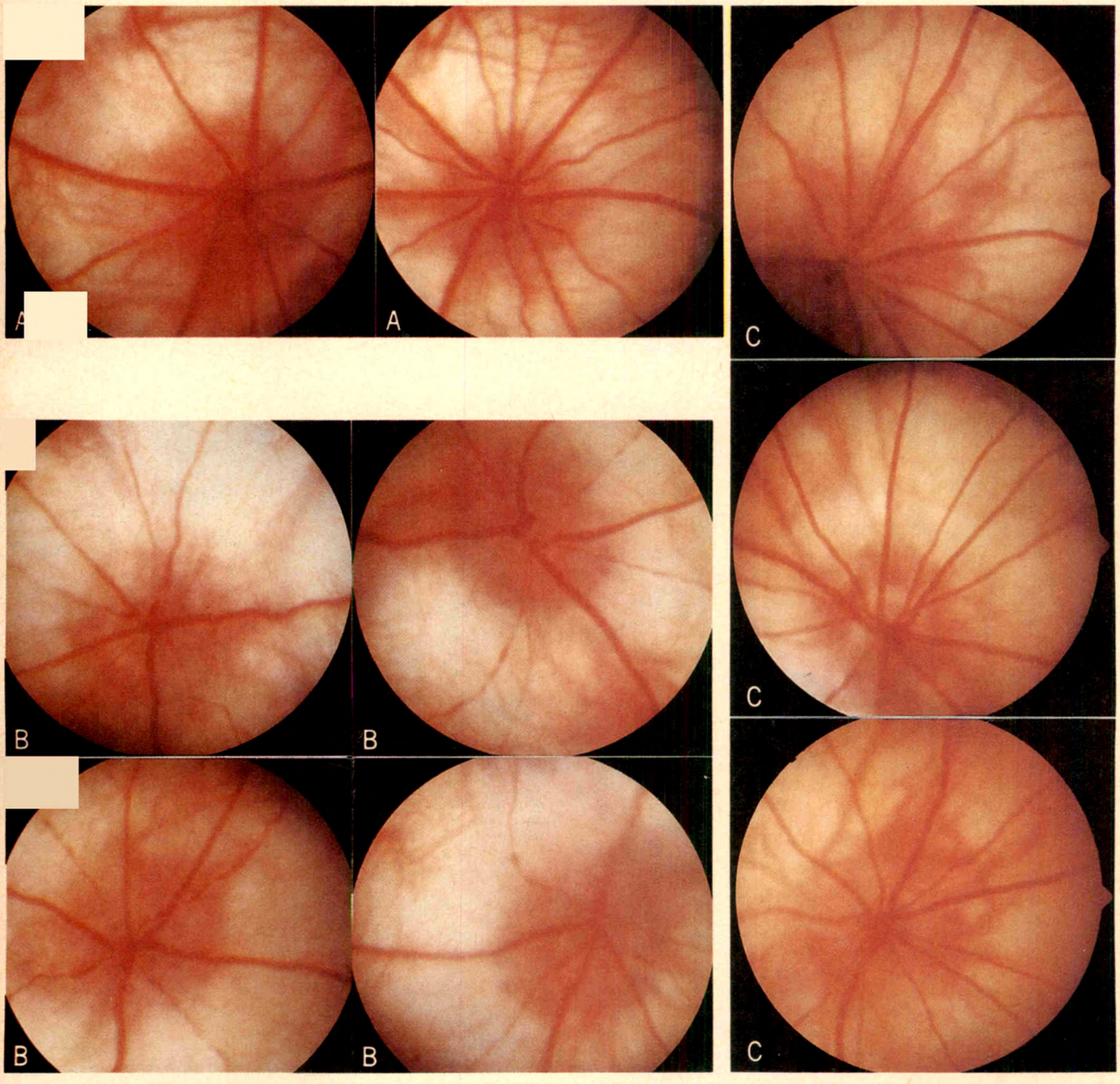

FIGURE 7: A, Normal ocular fundus of nonhypertensive WKY control rat. Note the veins (large diameter) and the arterioles (smaller diameter). **B,** Severe arteriolar vasoconstriction and development of aneurysm-like caliber irregularities in untreated 19-month-old spontaneously hypertensive rats. There is absence of discernible alterations in width and structure of the veins. **C,** Complete prevention of arteriolar spasm and aneurysm-like caliber irregularities in 19-month-old spontaneously hypertensive rats by long-term treatment with Ca^{++} antagonists over 18 months. **Top,** Treated with daily oral dose of verapamil (100 to 150 mg/kg) in diet calculated from food consumption. **Middle,** Treated with daily dose of nitrendipine (2 × 100 mg/kg) via stomach tube. **Bottom,** Treated with daily dose of nisoldipine (2 × 100 mg/kg) via stomach tube.

Accordingly, our ophthalmoscopic photographs of the ocular fundus of several series of untreated 19-month-old hypertensive rats revealed an incidence of aneurysm-like caliber irregularities of 75 to 85%.

With the use of Ca^{++} antagonists, however, all these severe arteriolar changes could be totally prevented in the overwhelming majority of hypertensive rats (Fig. 7C). In fact, the ocular arterioles of 60 Ca^{++}-antagonist–treated SHRs kept in the physiologic blood pressure range over 18 months showed no constriction, and showed minor luminal irregularities in only a few cases. The order of protective potency of the Ca^{++} antagonists tested to date over 18 months is nitrendipine = nisoldipine >verapamil (Fig. 8).

It is interesting to note that, even in the late stage of untreated hypertension, the 19-month-old animals still responded to single oral doses of Ca^{++} antagonists (100 mg/kg of nifedipine or nitrendipine) not only with a steep fall in blood pressure, but also with a rapid dilation of the constricted ocular arterioles. However, the aneurysm-like luminal protuberances did not disappear acutely. This indicates that a large part of the arteriolar narrowing in the ocular fundus is of spastic rather than sclerotic nature, whereas the aneurysms probably reflect a more pronounced structural alteration of the arteriolar walls.

In untreated hypertensive rats, larger arteries with thicker media always undergo still more spectacular changes than do the ocular arterioles. In other words, approximately the same time at which the arterioles develop aneurysms, the larger arteries exhibit arteriosclerosis. This is most dramatic in the mesenteric artery and its branches. Here severe media calcification with enormous wall thickening, partial or total luminal obliteration and ischemic damage of the gut were common findings (Fig. 9A and B). Again, all these pathologic changes of the arterial wall structure could be totally prevented by our Ca^{++}-antagonistic long-term prophylaxis over 18 months (Fig. 9C). Interest-

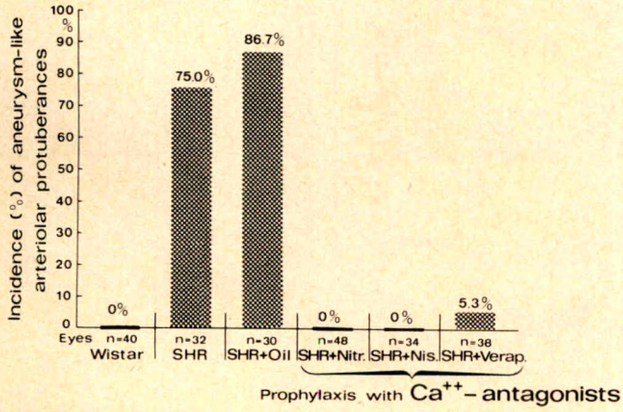

FIGURE 8. Ophthalmoscopic assessment of aneurysm-like luminal irregularities of the retinal arterioles in 19-month-old normotensive control Wistar Kyoto rats, in 19-month-old spontaneously hypertensive rats (SHRs) without Ca^{++}-antagonist treatment and in 19-month-old SHRs at the end of prophylactic administration of nitrendipine (Nitr.), nisoldipine (Nis.) or verapamil (Verap.) over 18 months. Incidence (%) = the number of eyes with arteriolar protuberbances in the ocular fundus in relation to the total number of eyes in each group. Because the SHRs were given nitrendipine and nisoldipine in an oil solution, an additional control group of 30 SHRs was formed in which the animals received corresponding quantities of pure oil without nitrendipine and nisoldipine ("oil") over 18 months.

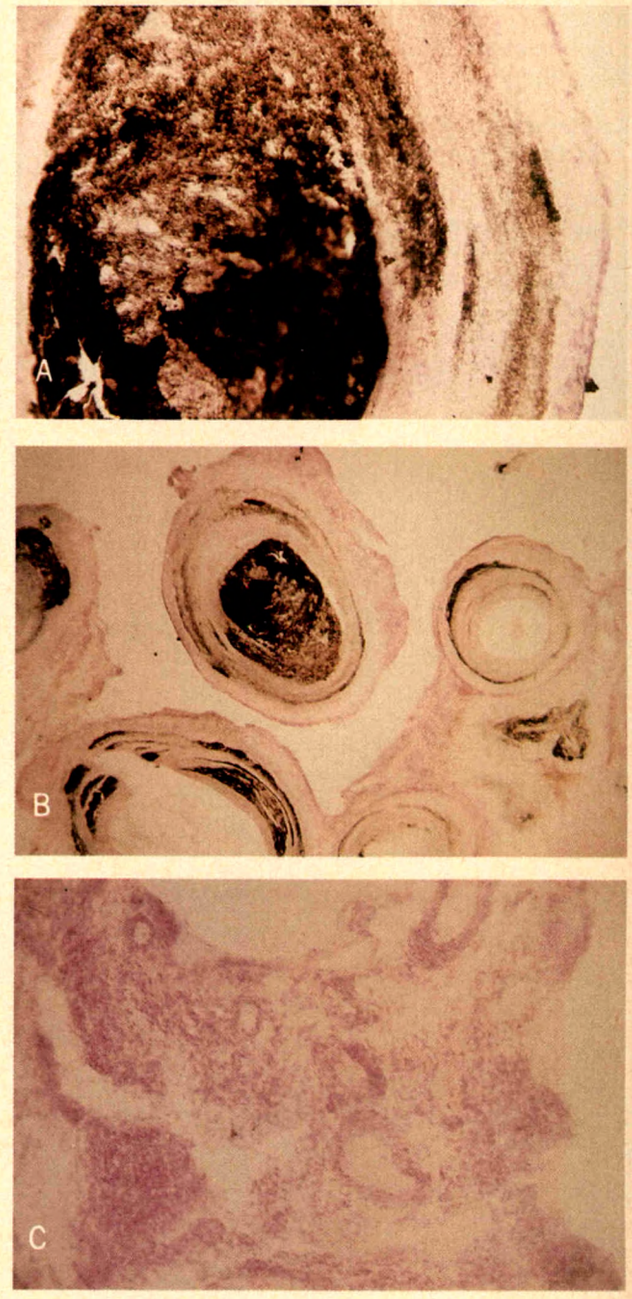

FIGURE 9. Antiarteriosclerotic long-term protection of spontaneously hypertensive rats (SHRs) demonstrated in the mesenteric artery and its branches. **A** and **B,** SHRs *without* Ca^{++}-antagonist treatment over 19 months. Without prophylaxis, complete or partial obliteration of the arterial lumen occurs in most mesenteric vessels. Simultaneously, calcific encrustations and enormous thickening of the arterial walls regularly develop. **C,** SHR after prophylactic long-term treatment with nitrendipine (2 × 100 mg/kg orally/day) over an observation period of 18 months. Complete preservation of structural integrity, i.e., no calcification, luminal narrowing or wall thickening of the mesenteric artery and its branches. Among a total of 60 Ca^{++}-antagonist-protected SHRs, there was no significant arterial damage. For visualization of tissue calcium as black areas, von Kossa's technique was applied, followed by additional staining with Nuclear Fast Red (Merck).

ingly, the mesenteric arterial walls, which always accumulate particularly great amounts of Ca^{++} during untreated hypertension (Fig. 6), also underwent the most dramatic morphologic alterations ever seen in our studies on hypertensive rats. Conversely, the antiarteriosclerotic prophylaxis with Ca^{++} antagonists was most obvious in this particular section of systemic circulation.

Prevention of Experimental Arteriosclerosis by Calcium Antagonists in Normotensive Rats

There is ample evidence that the anticalcinotic or antiarteriosclerotic efficacy of Ca^{++} antagonists is not only a simple consequence of their antihypertensive action, but may also manifest itself independently of any appreciable blood pressure change. Our first results were reported in 1971 in a presentation entitled "Inhibition of arteriosclerotic vascular lesions by prophylactic treatment with $MgCl_2$, KCl and organic Ca^{++} antagonists: quantitative studies with ^{45}Ca in rats."[32] Since then we have incessantly called attention to the vasoprotective properties that Ca^{++} antagonists can exert experimentally against various types of Ca^{++}-induced arterial damage. Our studies[1,28–30,32,33] led to the unconventional working hypothesis that excessive Ca^{++} incorporation into the arterial walls is a primary causative factor in the pathogenesis of arteriosclerosis, rather than merely a concomitant or subsequent phenomenon. Thus, we have found that all major risk factors that favor human arteriosclerosis (advanced age, diabetes, hypertension, excessive doses of dihydrotachysterol, vitamin D_3 and nicotine) are capable of enhancing arterial Ca^{++} uptake in healthy rats, and thereby facilitate or produce severe calcific alterations of the arterial walls. Conversely, suitable Ca^{++} antagonists have proved capable of protecting the arterial walls against calcinosis and structural damage. If such risk factors are acting in combination (for instance, nicotine plus vitamin D_3), tremendous degrees of deleterious arterial Ca^{++} accumulation can be attained within a few days in spite of little or no increase in blood pressure.

Figure 10A demonstrates the outstanding efficacy of diltiazem in inhibiting vitamin D_3-induced coronary calcinosis. Under the influence of vitamin D_3 alone, the Ca^{++} content of the coronary wall tissue of rats rose from 12 to 220 mmol/kg dry weight. With diltiazem, the effect of vitamin D_3 was completely neutralized.

To visualize the prevention of experimental coronary calcinosis by Ca^{++} antagonists, we also made use of histochemical techniques, particularly von Kossa's

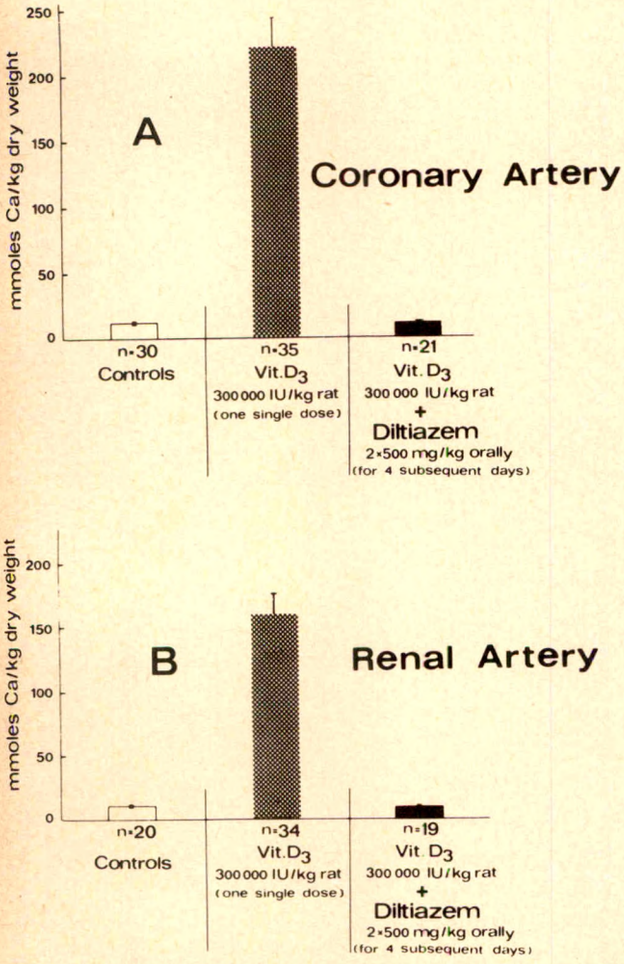

FIGURE 10. A, Oral administration of 2 × 500 mg diltiazem/kg body weight to rats for 4 consecutive days completely neutralizes the tremendous stimulation of Ca^{++} uptake into the coronary wall that otherwise would occur within 4 days after intramuscular injection of vitamin D_3 (300,000 IU/kg). **B,** Same observations as in **A** made on the rat renal arteries. Under the present experimental conditions, the relatively high oral doses of diltiazem were well tolerated during 4 days without any discernible negative side effects. Reprinted from Fleckenstein et al.[29]

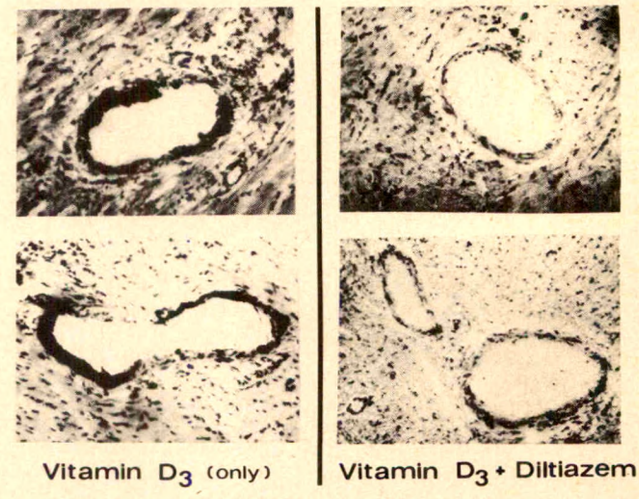

FIGURE 11. The 2 histological sections, **left,** show excessive Ca^{++} accumulation in the wall of rat coronary artery branches 4 days after 1 intramuscular injection of 300,000 IU vitamin D_3/kg body weight. Tissue calcinosis is visualized in the form of black areas with von Kossa's histochemical staining technique.[34] In contrast, calcinosis is totally absent in the 2 sections, **right,** originating from rats that had received diltiazem (2 × 500 mg/kg orally with a stomach tube) for 4 consecutive days after 1 intramuscular injection of 300,000 IU vitamin D_3/kg body weight. This treatment completely neutralizes the vitamin D_3 effects (see also Figure 10A). Reprinted from Fleckenstein et al.[29]

stain for tissue Ca^{++}.[34] Figure 11 shows some typical results. In the absence of diltiazem, the coronary arterial walls responded to vitamin D_3 with massive calcification and severe structural damage. In contrast, by simultaneous administration of diltiazem, the formation of black Ca^{++} deposits in the coronary smooth musculature could be totally prevented.

Under the influence of vitamin D_3 (in the given dose), the plasma Ca^{++} concentration increased by roughly 50% whether diltiazem had been given or not; however, with diltiazem the coronary wall tissue was shielded from excessive Ca^{++} uptake. This can be realized even by simple stereomicroscopic inspection of the coronary arteries in situ (Fig. 12).

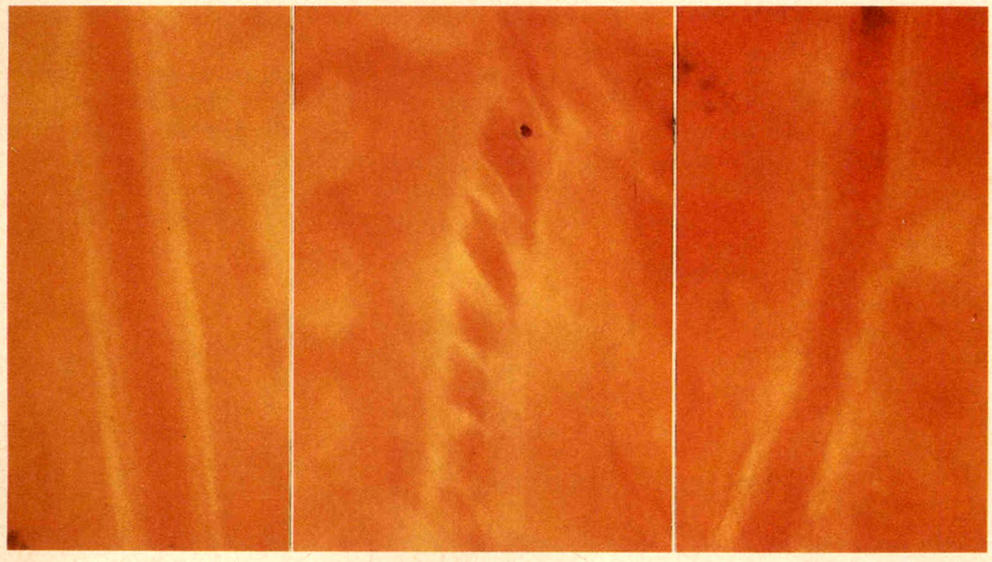

FIGURE 12. A massive calcinosis of the coronary stem arteries is produced in normotensive rats by the combination of 1 intramuscular injection of vitamin D_3 (300,000 IU/kg) with daily oral doses of nicotine (2 × 25 mg /kg) for 4 consecutive days. In these cases, the calcification of the coronary wall tissue is so spectacular that macroscopically discernible spiral plaques appear regularly within 4 days. However, with diltiazem (2 × 50 mg/kg) subcutaneously for 4 days, excessive Ca^{++} uptake and serious damage are prevented.

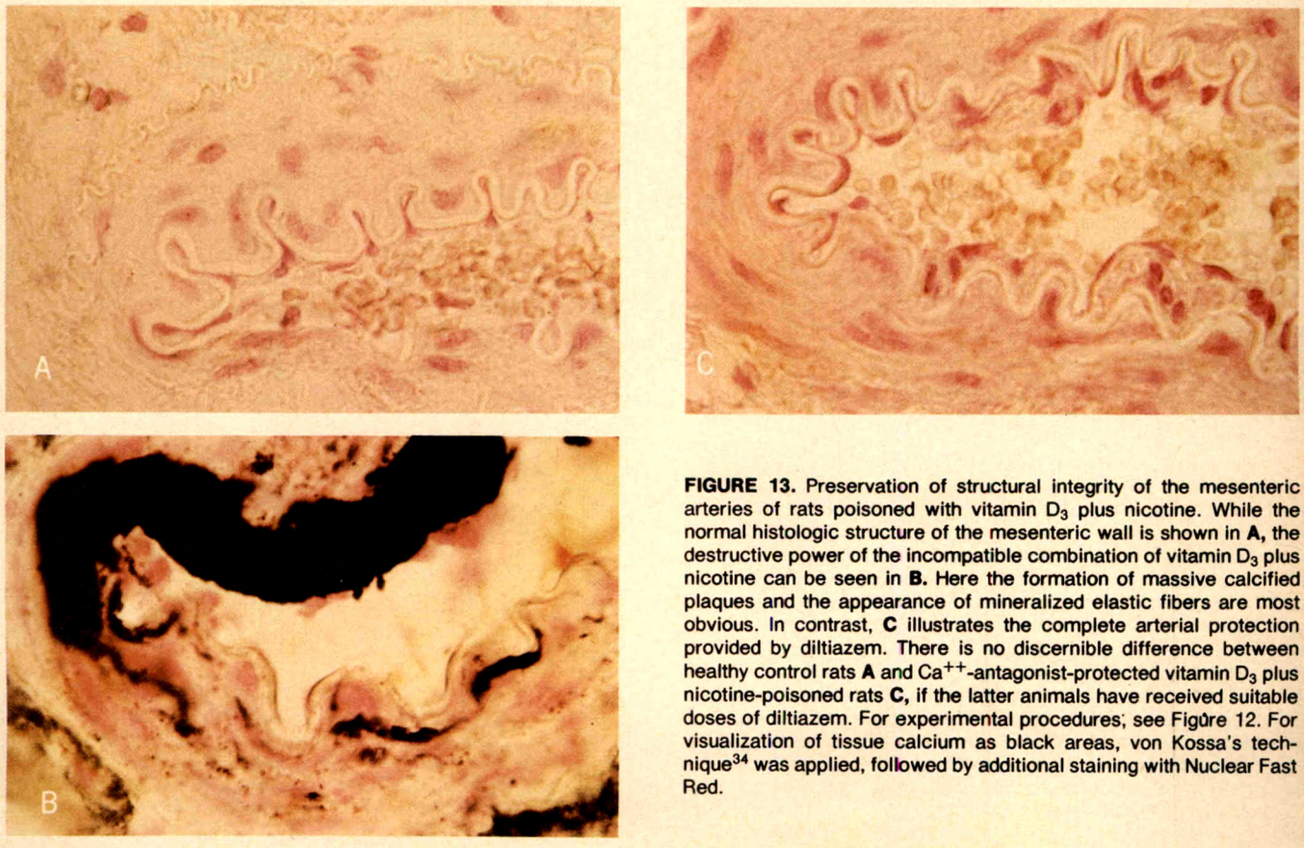

FIGURE 13. Preservation of structural integrity of the mesenteric arteries of rats poisoned with vitamin D_3 plus nicotine. While the normal histologic structure of the mesenteric wall is shown in **A,** the destructive power of the incompatible combination of vitamin D_3 plus nicotine can be seen in **B.** Here the formation of massive calcified plaques and the appearance of mineralized elastic fibers are most obvious. In contrast, **C** illustrates the complete arterial protection provided by diltiazem. There is no discernible difference between healthy control rats **A** and Ca^{++}-antagonist-protected vitamin D_3 plus nicotine-poisoned rats **C,** if the latter animals have received suitable doses of diltiazem. For experimental procedures; see Figure 12. For visualization of tissue calcium as black areas, von Kossa's technique[34] was applied, followed by additional staining with Nuclear Fast Red.

The anticalcinotic action of diltiazem is not restricted to the coronary vasculature, because the aortic, cerebral, mesenteric and renal (Fig. 10B) arterial walls were similarly protected by prophylactic diltiazem treatment. Figure 13B shows the typical media calcification of the mesenteric artery of a rat under the influence of vitamin D_3 and nicotine. Apart from calcified elastic fibers, the most spectacular change consisted of the development of massive calcific plaques. With diltiazem, however, the structural integrity of the mesenteric wall of the vitamin D_3-plus-nicotine–treated rats was fully preserved (Fig. 13C). In a series of more than 40 diltiazem-protected rats, in none did an appreciable aberration from the normal structure of the mesenteric wall (Fig. 13A) occur. Table I summarizes our studies on rats, in which the anticalcinotic efficacy of various Ca^{++} antagonists has been established under different experimental conditions.

In this context we emphasize that vitamin D_3-poisoned rats not only suffer from excessive Ca^{++} uptake into the arterial walls, but also accumulate cytotoxic amounts of Ca^{++} elsewhere,[37] e.g., in heart, kidney, intestinal smooth muscle (Figs. 14A and 15A). Again, suitable Ca^{++} antagonists (for instance, verapamil and diltiazem) provided a highly efficient anticalcinotic tissue protection. Figures 14B and 15B demonstrate the preservation of renal and intestinal integrity with diltiazem. Corresponding analytical data on the prevention of renal and intestinal Ca^{++} overload by diltiazem are shown in Figure 16.

In summary, Ca^{++} antagonists have been used to date in vascular therapy for *acute* functional vasodilation and spasmolytic purposes. The primary aim has been to improve, as quickly as possible, the blood supply to the heart and other organs by removal of purely functional obstacles (spasms) or by enlargement of collaterals and partially obliterated arteriosclerotic vessels. However, in the present context there is a question of much greater medical significance. Are these drugs also capable of exerting long-term anticalcinotic and antiarteriosclerotic effects, and can they,

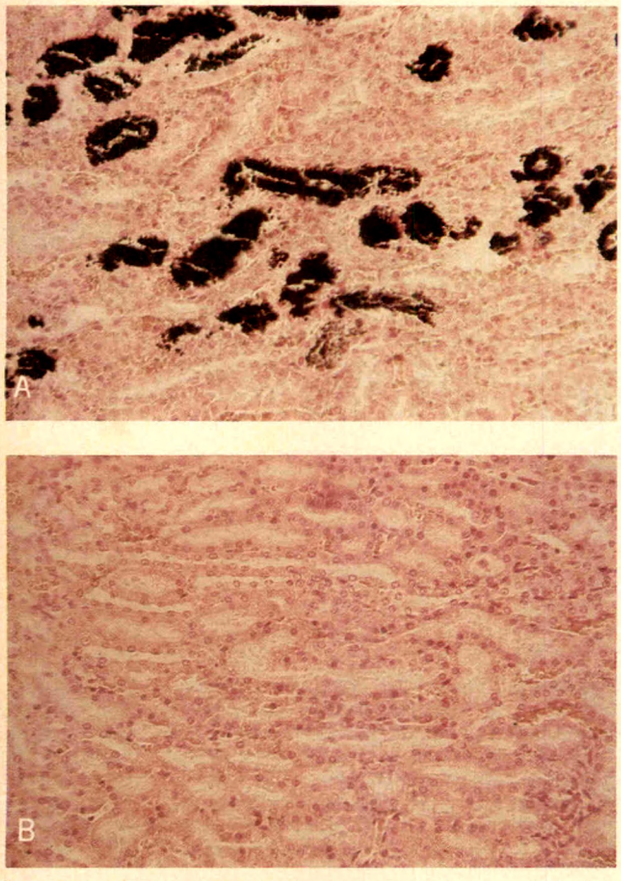

FIGURE 14. A, Severe renal calcification and tissue damage produced by combined administration of vitamin D_3 and nicotine, according to the procedure described in Figure 12. **B,** Complete anticalcinotic renal protection with diltiazem (dosage as in Figure 12). For visualization of tissue calcium as black areas, von Kossa's technique[34] was applied, followed by additional staining with Nuclear Fast Red.

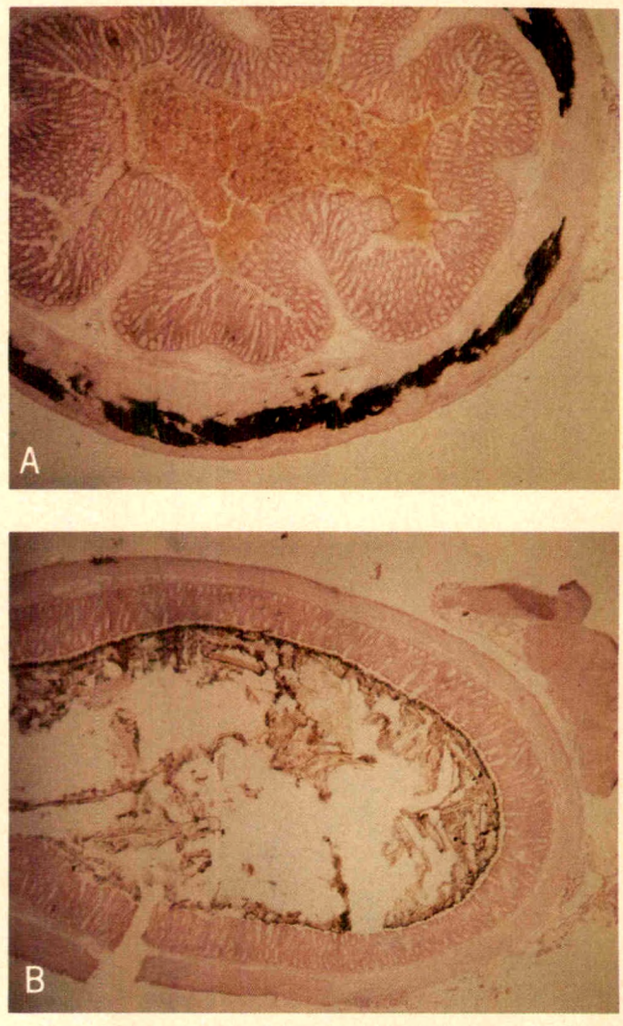

FIGURE 15. A, Calcification of intestinal smooth muscle produced by combined administration of vitamin D_3 plus nicotine according to the procedure described in Figures 12 to 14. **B,** Complete protection with diltiazem of intestinal smooth musculature against calcific necrotization (dosage as in Fig. 12). For visualization of tissue calcium as black areas, von Kossa's technique[34] was applied, followed by additional staining with Nuclear Fast Red.

TABLE I Types of Arterial Calcinosis Studied in Experiments on Rats

Type of Arterial Calcinosis	Effective Ca^{++} Antagonists Examined	References
Intoxication with dihydrotachysterol (AT 10) or vitamin D_3	Verapamil, diltiazem	1,3,28–30,32,33
Hereditary spontaneous hypertension	Nifedipine, nisoldipine, nitrendipine, nimodipine, verapamil	1,3,12,27–30
Advanced age	Verapamil	28,29
Alloxan diabetes	Verapamil	1,3,28,29
Chronic oral administration of nicotine*	Nifedipine, verapamil, diltiazem	28
Combined administration of vitamin D_3* plus nicotine	Diltiazem, verapamil	28

* See also the recent abstracts of our research group: Naunyn-Schmiedebergs Arch Path Pharmacol 1984;325:R43, Pflügers Arch ges Physiol 1984;400:R25 and J Mol Cell Cardiol 1984;16:suppl 2:64.

in this way, counteract vascular damage at its roots? This would mean that the Ca^{++} antagonists not only afford symptomatic improvement, but also interfere with the fundamental pathogenic process of excessive arterial Ca^{++} engulfment and its destructive consequences.

Spontaneous hypertension in rats represents a particularly interesting model in which the complexity of the arterial protection by Ca^{++} antagonists can be visualized. Obviously, *chronic hypertension* maintained over 18 months is closely linked with the development of severe arteriosclerotic lesions in systemic arteries (particularly the mesenteric artery). Suitable Ca^{++} antagonists prevent both essential hypertension and associated arterial damage.

However, progressive arterial Ca^{++} overload also occurs in aging normotensive rats, and can be experimentally enhanced at constant normal blood pressure by the well-known "coronary risk factors" (high doses of nicotine, dihydrotachysterol, vitamin D_3 or alloxan-induced diabetes). Ca^{++} antagonists interfere even in these cases with destructive Ca^{++} overload of the arterial walls and other organs. In other words, vascular protection by Ca^{++} antagonists seems to be exerted in a dual way, namely, by a superposition of antihypertensive and anticalcinotic effects.

All these experimental observations encourage a broader use of Ca^{++} antagonists in human antihypertensive therapy, particularly at an advanced age as proposed by Bühler[35] and Laragh.[36] Although clinical evidence of antiarteriosclerotic properties for Ca^{++} antagonists is still missing, further long-term treatment of hypertension with Ca^{++} antagonists will certainly create favorable conditions for parallel studies on human arteriosclerosis.

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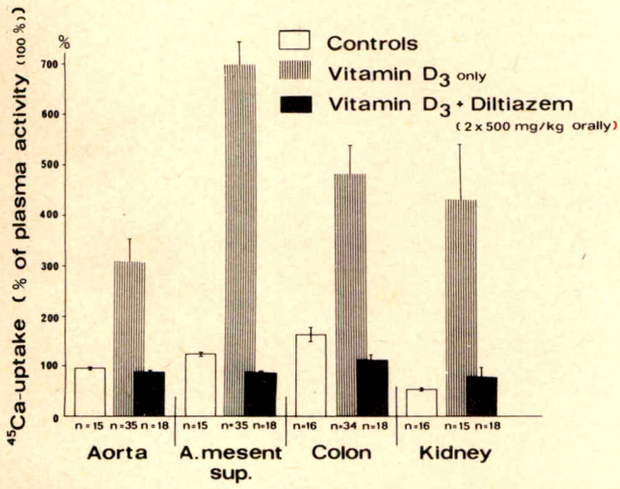

FIGURE 16. Inhibition of vitamin D_3-stimulated net radio-labeled calcium uptake into the walls of rat aorta and mesenteric artery by treatment with oral diltiazem. Simultaneously with inhibition of arterial Ca-45 incorporation, the vitamin D_3-induced calcinosis of renal cortex and colon (flexura dextra) is totally prevented. The specimens of myocardium, aorta, mesenteric artery, kidney and colon analyzed for Ca-45 uptake originated from the same animals. Experimental procedure as in Figure 10. Determination of the net Ca-45 uptake into the different organs was carried out 6 hours after intraperitoneal injection of 10 μCi Ca-45/kg body weight. Reprinted from Fleckenstein.[1]

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Experimental Chronic Cerebrovascular Spasm in the Monkey: An Assessment of the Functional Changes in the Cerebral Arteries and Their Protection by Diltiazem

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The structure and function of cerebral arteries obtained from a monkey model of chronic cerebral vascular spasm 5 days after hemorrhage have been examined. Narrowing of the larger cerebral arteries demonstrated by angiography at all sites of measurement seems to be due primarily to an increased wall rigidity associated with cellular damage, the resultant inflammatory response and large, long-lasting spontaneous increases in muscle tone. Changes in agonist sensitivity were extremely variable. The reduction of contractility of the vessel wall to a mean of 30% of control diminished the consequence of any changes in active tone characteristics. Neurogenic control on the side of the lesion was remarkably depressed.

When treated with diltiazem, beginning 1 day before induction of hemorrhage and continuing to the time of sacrifice, arterial diameter was reduced at only 1 of the 6 standard sites of measurement and then by only a small amount. Neurologic effects invariably seen in the untreated monkeys were prevented by diltiazem. Many of the changes in the artery wall, including structural alterations, were diminished by the drug. Abnormal spontaneous myogenic tone was present but was less in the diltiazem-treated group; however, nerve damage and its functional consequences were not prevented. It is concluded that diltiazem, presumably by preventing the accumulation of intracellular calcium within the cell, prevents the initial events in the evolution of chronic cerebrovasospasm or narrowing. This is probably achieved by a diminishing of the direct vasoconstrictor effects and the toxicity of putative spasmogens released from blood clots, nerves and the brain on the vascular smooth muscle, thus interrupting the sequence leading to pathologic change.

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We studied the chronic cerebrovascular vasospasm that developed after subarachnoid hemorrhage was induced in monkeys (*Macaca nemistrina*). This model resembles human disease because the vasospasm shows a prolonged course extending over several weeks, is diffuse and mainly unilateral, is invariably associated with a neurologic defect[1] and, in the established state, is minimally responsive to vasodilators.[2]

We attempted to test as many of the proposed causes of cerebral vasospasm (some of which are not mutually exclusive) as possible in this study. They include (1) active vascular smooth muscle contraction due to the localized and persistent effects of vasoconstrictor substances released from tissues and blood clots,[3–10] (2) vessel hyperreactivity associated with denervation hypersensitivity, resulting from the now well-established damage to perivascular sympathetic nerves[11–13] and (3) structural changes associated with thickening and decreased distensibility of the artery wall; these changes are presumed to arise from damage caused by arterial rupture and from toxic effects of high concentrations of a variety of vasoactive substances.[14–17]

There are other possible factors that might contribute to the overall narrowing that have not been formally proposed as causes of vasospasm. They include (1) overactivity of sympathetic adrenergic vasoconstrictor nerves; the large cerebral arteries are surrounded by a dense adrenergic axonal plexus and although the physiologic response to their activity is usually considered poor, its influence may be exaggerated by other associated changes,[18] (2) decreased activity of the vasodilator innervation; present evidence suggests that these nerves probably release both acetylcholine and vasoactive intestinal polypeptide, but the physiologic role of this neural system is not understood,[19,20] (3)

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loss of vascular endothelium; it is probable that the endothelium in cerebral arteries, like that in other blood vessels, releases relaxing factors[21] and endothelial-induced vascular relaxation is sensitive to even low levels of trauma and (4) an exaggerated cerebrovascular smooth muscle response to stretch; a myogenic response to wall stretch is a physiologic characteristic of middle and smaller cerebral arteries.

The technique of causing subarachnoid hemorrhage in the monkey was previously described.[1] Under anesthesia, a 0.4-mm needle with a percutaneous suture is placed through the intracranial part of the internal carotid artery and removed 24 hours later. Control measurements of arterial pressure from arterial puncture are made, and angiography and neurologic examination are performed before needle removal and also on the fifth or sixth day, immediately before the animal is killed. The animal is then bled and the brain is removed and placed in a bath of Krebs bicarbonate solution of the following composition in m*M*: sodium, 144.23; potassium, 4.9; calcium, 1.6; magnesium, 1.2; chloride, 126.7; HCO_3, 25; SO_4^{2-}, 1.19; glucose, 11.1; and ethylenediaminetetraacetic acid, 0.024, equilibrated with 95% O_2-5% CO_2. The circle of Willis and its main branches are dissected free, and corresponding segments from the 2 sides are examined and compared for structural and functional change.

In this study, the following parameters were measured: passive length-tension relation, active wall tension response to electrical field stimulation of vasoconstrictor and vasodilator nerves, responsiveness and sensitivity to various agonists (both constrictor and dilator) and vessel dimensions (internal diameter and wall thickness). Morphologic measurements included light and electron microscopy and catecholamine histofluorescence. In addition, neuronal uptake of tritium-labeled norepinephrine and choline acetyltransferase activity of the arterial wall were determined.

We also investigated the possible protective effects of diltiazem, a calcium-channel blocker. Diltiazem is a benzothiazepin derivative and is thus in a different chemical class from other drugs with similar action, such as nifedipine and nimodipine, which are dihydropyridines, and verapamil, which is related to papaverine. In an in vitro study of rabbit arteries, diltiazem was found to influence cerebrovascular tone mediated through potential-sensitive as well as receptor-operated channels. Higher concentrations were needed to inhibit the myogenic response in these arteries, which probably involves different calcium-entry mechanisms and contributes to cerebrovascular autoregulation.[22]

It seemed reasonable to us when planning these experiments that many of the causes of vasospasm that have been proposed might be antagonized by diltiazem. The initial action of endogenously released substances, which in high concentrations might lead to cellular damage and chronic spastic state, probably involves calcium entry into vascular smooth muscle cells. A partial list of possible spasmogens, proposed mainly on the basis of short-term animal experiments, includes blood and blood products, hemoglobin, histamine, potassium, norepinephrine, prostaglandins and serotonin. Whether the action of most of these substances on monkey cerebral vessels is diltiazem-sensitive has not been established.

Our primary objective was to test the possibility that an early causal step in vasospasm involves calcium entry into the smooth muscle cell and that this step might be antagonized by diltiazem. Monkeys were pretreated with diltiazem, 25 mg/kg 2 times a day, a dose that does not affect arterial pressure in the monkey. We realize that this regimen is not clinically relevant, particularly in an emergency setting when diltiazem could only be administered after the hemorrhage had occurred. However, our main objective was to investigate the potential for drug protection.

We previously reported that diltiazem markedly ameliorates the arterial narrowing measured at 6 standard sites on the angiogram.[23] Without treatment, the mean "most constricted" site in the series was 22% of the prehemorrhagic diameter. After diltiazem, this value was 84%—a difference that was very significant ($p < 0.001$). The most constricted site is probably the one of greatest clinical significance. Although there was still significant narrowing at this site after diltiazem ($p < 0.01$), the reduction in diameter was relatively small. At only 1 standard position of measurement in the diltiazem-treated group (the distal site on the middle cerebral artery) was the diameter of the lesion side less than the preinsult diameter ($p < 0.05$). In the diltiazem-treated group, no changes were found in any animal on neurologic examination; in contrast, consistent neurologic abnormalities were found in the untreated group.

Functional Changes in the Cerebral Arteries Associated with Chronic Cerebral Vasospasm

The most consistent change in the larger cerebral arteries, and the one we feel contributed most to the luminal narrowing, was an increase in vessel wall rigidity, specifically an increased resistance to passive distension (Fig. 1). In most arterial segments, the passive tension-length curve was shifted to the left after hemorrhage on the lesion side compared with the contralateral side. The mean percentage increase in wall tension over the "physiologic range of stress" based upon the Laplace transformation was about 450%. Although arterial wall thickness was minimally and inconsistently increased, it was insufficient to account for the increase in wall rigidity.

Spontaneous excursions of tone were seen in large and small arteries, including a pial artery of about 150μm outside diameter in the distal middle cerebral artery bed, especially on the lesion side. Tone development was large, often approximating the maximal level that the artery could attain, and frequently lasted more than 1 hour. It was dependent on calcium entry into the cell, presumably into vascular smooth cells, from the extracellular space. The capacity of the arterial segments to develop an increase in wall tension in response to a variety of agents was very markedly reduced on the lesion side—on average, to about 30%

of the contralateral side. The most likely explanation for this was damage to the smooth muscle cells. The greatest reduction in contractility in vitro was associated with the greatest arterial narrowing found on angiography. This relation might imply that spasm/narrowing occurred in those vessels that were damaged the most, and that vasopasm is unlikely to be associated with a large component of active vascular tone with or without associated hypersensitivity.

Changes in agonist sensitivity were extremely variable and were often difficult to assess because of the irregular patterns of response and the frequent and prolonged spontaneous increases in tone that were recorded, particularly on the side of the experimental damage. (In vitro sensitivity in the pharmacologic sense can only be satisfactorily measured from a baseline of 0 or at least low-level tone.) There was a trend toward selective increase in sensitivity to serotonin compared with norepinephrine. However, whatever changes in reactivity were present, their functional consequence would be expected to be relatively small, because the ability of the artery wall to contract was very significantly reduced.

Efferent nerve integrity was assessed by biochemical and functional in vitro study. All measurements—the responses to electrical field stimulation, choline acetyltransferase and tritium-labeled norepinephrine neuronal uptake—indicated a dramatic and consistent depression of both constrictor and dilator neuronal activity. We attempted to determine endothelial influences on smooth muscle tone in vitro by measuring the dilator response to acetylcholine after tone had been elevated. Dilation was invariably absent in arteries from both sides—although the arteries invariably relaxed in response to such vasodilators as papaverine and nitrate. The fact that the acetylcholine response is readily eliminated by handling—by such trivial injury as contact between adjacent endothelial surfaces—and was only occasionally and weakly encountered in sham-operated controls precludes a clear-cut association between loss of endothelial-based dilation and subarachnoid hemorrhage. However, the consistent observation of marked structural endothelial damage, which will be discussed, especially in the arteries on the side of experimental hemorrhage, strongly implies that endothelial-based dilation would not occur in vivo.

Structural Changes in the Cerebral Arteries Associated with Chronic Cerebral Vasospasm

In many respects, the structural changes in the wall correlate with the functional changes just described. Ring arterial segments were taken from comparable sites on the terminal part of the internal carotid artery and the middle and anterior communicating cerebral arteries. In addition, whole-mount segments from those arteries close to the base of the brain were processed for specific catecholamine fluorescence microscopy. In vessels taken from nontreated monkeys, clots were found adhering to the artery wall, particularly the anterior segment. The subjacent arterial wall was grossly abnormal; it was edematous with inflammatory cell infiltration, particularly of the adventitia and around the perivascular nerves, mainly by macrophages and fibroblasts. Almost invariably, there was separation of the internal elastic lamina and degenerative changes in the tunica media with vacuolation of the smooth muscle cells. There was also consistent separation of the tunica intima and subintimal tissues with subendothelial accumulation of fluid and cellular debris. Changes were relatively minor in the diltiazem-treated group; marked degeneration was not seen in the smooth muscle cells, although some vacuolation was encountered.

Diltiazem did not prevent loss of specific catecholamine fluorescence in adrenergic nerves on the lesion side. Large, intensely fluorescent nerve bundles were often seen proximal to the site of puncture. Beyond the area of damage, fluorescent nerves were infrequently seen; fluorescence intensity was markedly diminished, although changes were patchy. Using elec-

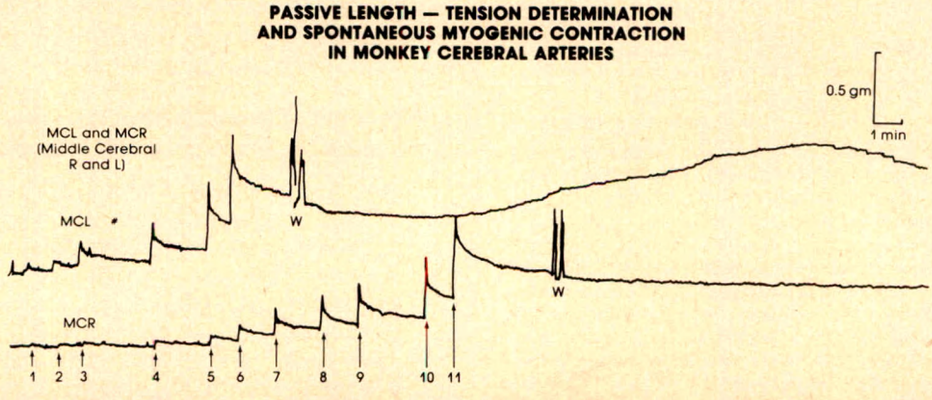

FIGURE 1. Experimental records from in vitro study of segments of middle cerebral arteries in the monkey. Five days previously, the monkeys experienced subarachnoid hemorrhage after experimental puncture of the left intracranial internal carotid artery. The record shows exaggerated increase in tension after standard increments of wall stretch in the left compared with the right side. It also shows a small, short, spontaneous increase in wall tension on the lesion but not on the contralateral side. These 2 phenomena represent the major consistent changes in the large cerebral arteries, which may be the major contributors to arterial narrowing. W = experimental artifact when physiologic saline in tissue bath was changed.

tron microscopy, we observed mixed perivascular nerve bundles that showed degenerative change.

These alterations are consistent with the increased rigidity of the arterial wall, the loss of contractility and the marked diminution of neurogenic reactivity that have already been described. We can only surmise that the abnormal myotonicity is related to minimal levels of damage of the vascular smooth muscle cells.

Assessment of the Contribution of Various Arterial Changes to Luminal Narrowing

It is quite clear that the extreme arterial narrowing called spasm could be the consequence of one or more of the changes already described. In this study, the arteries were only examined on the fifth or sixth day after hemorrhage. Because different arterial attributes were assessed in anatomically separate but adjacent segments, only a fragmentary idea of the changes that take place in these vessels can be formed and then only for the day the animal was killed. Any generalization necessitates considerable extrapolation.

The increase in wall stiffness, the hypersensitivity to agonists, the loss of dilator nerve influence and possibly the absence of endothelial-derived dilation should all be considered as possible causes of arterial narrowing. In addition, there may be changes that we have not measured—for example, those that only occur in situ—in which local constrictor influences could be at work. Thus we cannot, on the basis of these experiments, reach any definitive conclusion with respect to the dominant cause and the relative importance of any contributing factors. However, certain inferences can be made from the mean changes in wall

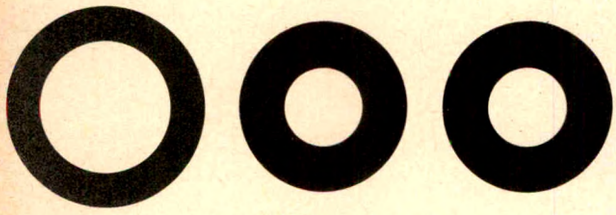

FIGURE 2. Diagrammatic representation of cross section of artery with a wall:lumen ratio of 1:4 is shown, **left. Middle** shows the estimated consequence of a mean change in wall rigidity measured in the monkey series at a blood pressure equivalent to that experienced in the artery at the base of the brain in vivo. A 10% increase in wall mass was assumed. **Right** shows a vessel with changes similar to those depicted in the middle, but also showing the consequence of denervation hypersensitivity (× 3 increase) and a tone increase in response to vasoactive substances equivalent to 30% of maximal contraction (EC_{30}). All of these effects are attenuated by a simultaneous 70% loss of contractility. These mean alterations were found in the large cerebral arteries of the monkeys in this study. It is assumed that vascular smooth muscle cells shorten maximally by 30% of their length and that constriction occurs without changes in wall mass.

elasticity found in the control untreated monkey series, in conjunction with the protective effect of diltiazem. The *mean* change in elasticity alone would be expected to cause a reduction of internal arterial diameter of 40%. If such a narrowing occurred consistently throughout the resistance vessels of the arterial tree, flow would be reduced by about 80%. In particular segments, the increased rigidity would be responsible for an even greater narrowing. The diameter of the most constricted arterial segment in this series was narrowed by approximately 80%. In Figure 2 the changes in an artery associated with this change in elasticity, in which wall mass also increased by 10%, are shown. We found that abnormal myogenic tone was also marked; however, its consequence on wall tension is difficult to assess because the myogenic influence would be decreased by associated reductions in contractility. However, in most cases, we feel abnormal myogenic tone would have a significant influence on arterial diameter.

Figure 2 also shows the additional changes expected from the action of unspecified vasoactive substances that increase smooth muscle tone to an equivalent of 30% of its maximal capacity to contract. The effects of a hypersensitivity factor of × 3, which is probably greater than that associated with denervation in a vessel in which contractility is diminished by 70%, are included. If these approximations have any relevance at all to the intact state, it can be seen that the contribution of the alteration in elasticity is most influential in diminishing luminal diameter. It is assumed that these changes in wall tone take place without significant alteration in wall volume.

In the small pial vessels that we have studied —which are of the order of 150μ outside diameter—the most dominant change was an abnormal myogenic tone. However, because of the irregular and apparently random pattern, such changes were hard to quantitate and relate to the intact circulation. Their magnitude, however, does suggest that they would be of considerable consequence.

We can only speculate that the greater the distance from the initial injury and hemorrhage site—that is, the more distal along the arterial bed—the less important would be passive wall changes and, probably up to a point, the greater the influence of any active, particularly spontaneous, changes in tone.

Effect of Diltiazem on Structural and Functional Changes in Chronic Cerebral Vascular Spasm

Pretreatment with diltiazem greatly attenuated the arterial narrowing as assessed by angiography and prevented the associated neurologic defect.[23] Essentially, changes in cerebral arterial wall elasticity as assessed by the passive length-tension relation were averted. In several monkeys, these curves, which were derived from corresponding segments of the 2 sides, could virtually be superimposed. Neither change in wall thickness nor trend toward an increase was detected. The effect of the drug on these parameters was clear-cut and convincing. However, spontaneous changes in

myogenic activity were recorded that were very much greater on the lesion side compared with the opposite side and, in absolute terms, were sizable. Arterial wall contractility was to a large measure preserved in the diltiazem-treated group. Thus, the spontaneous changes in tone—if related to the capacity of the wall to contract—were diminished in the diltiazem-treated animals. It should be kept in mind that by the time arterial segments were examined in vitro, they had been removed from the animal for several hours and constantly bathed in Krebs bicarbonate saline solution. It seems likely that diltiazem present in the artery wall upon removal would have been washed out before the in vitro study. Because this myogenic activity was depressed by diltiazem added to the tissue bath, it is probable that it would be inhibited in vivo. Nevertheless, the exact role of this phenomenon in vasospasm is enigmatic. It is not the same as "physiologic" stretch-dependent tone, which is readily lost on handling and which shows a direct causal relation to wall tension.[24]

Changes in sensitivity to agonists did occur in the vessels from the diltiazem-treated monkeys and were extremely variable. Useful comparisons with the untreated monkey series could not be satisfactorily made because of this extraordinary variability. Diltiazem did not preserve neuronal function. The various indexes of neural control were all diminished and did not differ from the untreated series.

The structural changes in the artery wall were consistent with findings of the functional study. The fabric of the wall was far better preserved in the diltiazem-treated compared with the control group; however, the efferent nerve terminals were unprotected.

Evolution of Chronic Cerebral Vascular Spasm

We can only speculate regarding the series of events that culminates in the arterial change that we found on the fifth day of hemorrhage in this monkey model, when vasospasm seemed to be maximal (Table I). Unquestionably, during the hours just after hemorrhage, the cerebral arteries, particularly those at the base of the brain, are surrounded by many putative spasmogens. Their effect on vascular tone would depend almost exclusively on promoting the entry of calcium into the cytoplasm of the vascular smooth muscle cells from the extracellular space. The vasoactivity of most of these substances has been shown in acute in vivo and in vitro studies to be effective in causing a contraction of cerebral arteries that is susceptible to 1 calcium-channel blocker or another.[25–33] It seems reasonable, therefore, to conclude that the initial acute vasospasm (not demonstrated as yet in this model, but that would almost certainly occur and that has been consistently seen in other experimental preparations) is due to active vascular smooth muscle contraction resulting from the activity of such extrinsic substances. Actions of individual substances are probably augmented by synergistic effects and also by changes in the vascular smooth muscle cells themselves. The fact that the narrowing that occurs soon after subarachnoid hemorrhage can be reversed by vasodilator drugs[34] is consistent with such a proposition.

TABLE I Experimental Cerebrovascular Spasm (based mainly on studies of effects of experimental subarachnoid hemorrhage in the monkey)

Spasm	Acute (hours)	Chronic (days)
Cause	Spasmogens released from blood clot, nerves and tissues*	Inflammation of arterial wall, edema, fibrosis
Basis of narrowing	Exaggerated normal active muscle tone*	Increased wall rigidity and active, possibly abnormal, muscle tone*
	Dependent on extracellular calcium	Only active tone dependent on extracellular calcium

Hypothesized differences between 2 phases of vasospasm that occur in the monkey subsequent to experimental subarachnoid hemorrhage. We presume that the second vasospasm follows from the first.

* Possible sites of the protective action of diltiazem, leading to reduction in arterial narrowing.

This early period of true vasospasm presumably merges into a second phase when the changes in the arterial wall resulting from damage become prominent. These changes are probably caused by the high concentrations of vasoactive substances released from many sources, including nerves,[15,35] clots and possibly the brain, and by the reaction of the vascular wall to the ensuing damage, the consequences of which become progressively important. Thus, passive wall changes might be expected to dominate more and more with time. Once these latter processes are established, the resultant narrowing would not be expected to be influenced by vasodilator drugs.[34] Such an explanation is consistent with the biphasic time course of the disease[36] and with the slowly progressive and long-lasting phase of the clinical condition. This theory is also consistent with the well-established resistance of clinical vasospasm to therapeutic manipulation. The gradually progressive dominance of the passive changes associated with rigidity and fibrosis reflects what is seen at autopsy when cerebral arteries show perivascular medial and subendothelial fibrosis and other signs of resolved inflammatory reaction.[16]

We can only speculate that diltiazem is protective because it antagonizes the entry of calcium through channels involved in the physiologic control of vascular smooth muscle tone—potential-sensitive and receptor-operated channels.[37] This entry would be initiated by the vasoactive material present around the artery wall. Further, diltiazem might owe some of its action to its cellular protective potential. Our study of arterial wall change in experimental subarachnoid hemorrhage and the protective effect of diltiazem may help to explain the significant therapeutic effect of nimodipine in some patients with subarachnoid hemorrhage.[38] This latter study was limited in that it was restricted to neurologically normal patients and the severity of the vasospasm was not always assessed. Nevertheless, the finding is of major clinical interest.

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Hemodynamic Effects of Calcium Entry–Blocking Agents in Normal and Hypertensive Rats and Man

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To be considered ideal for the treatment of hypertension, a class of drugs should produce a maintained reduction of arterial pressure primarily through a fall in total peripheral resistance that is at least uniformly distributed through the organ circulations of the target organs of hypertensive vascular disease. Such drugs should be useful as monotherapeutic agents, should not expand the extracellular fluid compartment, should not reflexively stimulate the heart and vessels, should reverse the structural changes in the target organs without compromising function and, of course, should be relatively free of adverse effects. As a heterogeneous class of agents, the calcium entry–blocking drugs fulfill most of these criteria, although preliminary studies suggest that their effects on organ vascular resistances and on structural cardiovascular changes are highly variable. Thus, further vigorous investigation of these new agents is highly recommended.

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The calcium entry–blocking drugs have been widely used in the United States and throughout the world for a number of years for the treatment of patients with ischemic heart disease. Although they have been used over the past decade for the treatment of hypertension elsewhere in the world, they have not yet been approved for this indication by the U.S. Food and Drug Administration. This should stimulate a feeling of déjà vu in physicians who have been in practice during the past 10 to 15 years; it is reminiscent of the story of the β-adrenergic receptor–blocking drugs. A similar long period elapsed between the time they were used worldwide for the treatment of hypertension and when they were approved in the U.S. I have no doubt, however, that the calcium entry–blocking agents are being used as antihypertensive drugs in the U.S. today—presumably for those patients with coexisting ischemic heart disease and hypertension. As is well known, hypotension is the most consistent side effect shared by most of these compounds in patients who have been treated for coronary artery disease.

Hemodynamic Considerations

The hemodynamic hallmark of hypertension, and particularly essential hypertension, is an increased total peripheral resistance that seems to be uniformly distributed throughout all the vascular territories.[1,2] As the left ventricular (LV) afterload (i.e., the rising arterial pressure and total peripheral resistance) increases, the heart adapts by the development of a concentric form of LV hypertrophy.[3–5] Associated with this process is an increased myocardial oxygen consumption that is secondary to 2 factors: one is obviously the increased arterial pressure (in this instance, the systolic pressure); the other is the increased chamber diameter (i.e., the cardiac enlargement) that follows at an equal rate with the ever-increasing afterload.[1–8] Associated with the adaptive structural changes by the heart is the structural change of arteriolar thickening,[9] which is also associated with acceleration of an independent but closely interrelated process, atherosclerosis.[10,11]

In addition to these pathophysiologic considerations related to the progression of hypertensive cardiovascular disease, other physiologic changes are associated with antihypertensive therapy.[12,13] For example, we know that as most drugs reduce arterial pressure, intravascular (plasma) volume expands. There are some agents that are notable exceptions to this rule: diuretics (for obvious reasons), β-adrenergic receptor–blocking drugs, probably the angiotensin converting enzyme inhibitors and, most likely, the calcium entry–blocking drugs. This failure to expand intravascular volume is in contrast to the other classes of antihypertensive drugs (e.g., direct-acting vascular smooth muscle relaxants and adrenergic inhibitors)

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TABLE I The Ideal Antihypertensive

An ideal antihypertensive agent should reduce arterial pressure:
- by decreasing total peripheral resistance
- through uniform reduction of organ vascular resistances
- without
  - retaining extracellular fluid
  - reflexively stimulating the heart
- with regression of structural changes that do not impair
  - organ function
  - systemic performance

that must be used with diuretics. The diuretics prevent volume expansion and development of the so-called phenomenon of "pseudotolerance".[14,15] Even those agents that may not be associated with fluid volume retention will show enhanced effectiveness if prescribed together with a diuretic.[16] These observations explain the traditional first 2 steps of antihypertensive therapy: diuretics, followed by adrenergic inhibitors.[17–19] They also explain why the β blockers, angiotensin converting enzyme inhibitors and calcium entry–blockers have been used as first-step monotherapeutic agents for the treatment of hypertension.[20]

A second important factor that may be related to antihypertensive therapy is reflex cardiac stimulation, which occurs with those antihypertensive drugs that do not inhibit adrenergic input to the cardiovascular system.[12,13] For some as-yet-unexplained reason, this also is not generally associated with the angiotensin converting enzyme inhibitors,[21] angiotensin receptor inhibition[22] or certain calcium entry–blocking drugs.[23–25] This concept is important, because reflex cardiac stimulation will increase myocardial oxygen consumption, aortic flow acceleration and myocardial metabolism, and will thereby aggravate associated cardiac problems (e.g., coronary artery disease, myocardial infarction, congestive heart failure and dissecting aortic aneurysm).[26]

Therefore, an ideal antihypertensive agent should reduce arterial pressure primarily by decreasing total peripheral resistance associated with a relatively uniform decline in the vascular resistances in the major vascular territories of the body. However, this arteriolar dilation should ideally involve the primary target organs of the disease: the brain, heart and kidney. Moreover, this pressure reduction should be accomplished without secondary fluid retention or reflex stimulation of the heart. Further, if there is some regression in the associated hypertrophic structural changes without altering performance or function of the organs or the patient, we truly will have an ideal antihypertensive drug (Table I). The discussion that follows will be concerned with how well the calcium entry–blocking drugs measure up to these criteria.

Calcium Entry–Blocking Drugs

Some of the first studies that provided useful information concerning the antihypertensive and hemodynamic effects of the calcium entry–blocking drugs emanated from Italy. Olivari et al[23] reported data from 27 patients who were treated with nifedipine. After 3 weeks of therapy, the reduced arterial pressure was

TABLE II Antihypertensive Effects of Nifedipine in 27 Patients with Essential Hypertension Treated for 3 Weeks

Index	Control	Treatment
Mean arterial pressure (mm Hg)	140	120*
Heart rate (beats/min)	75	74
Cardiac index (liter/min/m^2)	3.6	4.1*
Stroke index (ml/beat/m^2)	49	55
Total peripheral resistance (dynes s cm^{-5})	1,766	1,281*
Plasma volume (ml)	3,149	3,049
Glomerular filtration rate (ml/min)	81	82
Plasma renin activity (ng/ml/hour)		
Supine	0.57	0.74
Standing	1.01	1.45

* Statistical significance at least at the $p < 0.05$ level.
Adapted from Olivari et al.[23]

not accompanied by a faster heart rate, although cardiac output was somewhat greater than pretreatment levels; the pressure reduction, therefore, was due to a fall in total peripheral resistance. In addition, there was no expansion of intravascular (plasma) volume, glomerular filtration rate was preserved and plasma renin activity was unchanged (Table II). Muiesan et al[24] compared the effects of verapamil (80 mg, 3 times a day) with nifedipine (10 mg, 3 times a day). A significant pressure reduction was observed with both agents in both the supine and standing positions, without producing orthostatic hypotension; there was no evidence of an increased heart rate (Table III). They also reported that with prolonged treatment, nifedipine increased circulating norepinephrine levels, although verapamil produced no change in supine and standing norepinephrine levels. In addition they found that plasma renin activity, aldosterone levels and plasma volume remained unchanged with prolonged treatment.

Perhaps these early findings explain why most investigators in Europe and Japan now use these agents as first-step monotherapy for treatment of hypertension, without observing fluid retention or reflex cardiac stimulation.[26–29] Muiesan et al[24] also compared 2 dosage levels of verapamil (80 and 160 mg, 3 times a day) with nifedipine (10 mg, 3 times a day) for a 2-month period (Table IV). At the higher verapamil dosage there was a further fall in pressure, which was unassociated with a faster heart rate. When responses to verapamil were compared with those in patients receiving nifedipine, there were no significant differences in plasma renin activity, although at the higher dosage of verapamil, norepinephrine levels (in the upright posture) seemed to be higher. These findings were substantially similar to a number of later reports from other centers.[25–27]

Safar et al[27] recently reported the immediate hemodynamic effects of diltiazem (0.2 mg/kg) in 11 patients with essential hypertension. After intravenous administration there was a significant fall in mean arterial pressure (from 120 to 109 mm Hg) and total peripheral

TABLE III Effects of Verapamil and Nifedipine in an 8-Day Study of Patients with Essential Hypertension

Index	Control		Verapamil (80 mg, 3 times a day)		Nifedipine (10 mg, 3 times a day)	
	Supine	Standing	Supine	Standing	Supine	Standing
Blood pressure (mm Hg)	164/106	161/111	141/91*	138/95*	138/90*	129/88*
Heart rate (beats/min)	74	84	74	81	76	96
Norepinephrine (ng/liter)	156	311	194	352	297*	500*
Epinephrine (ng/liter)	69	86	82	90	92	185*
Plasma renin activity (ng/ml/hour)	1.6	3.7	1.2	3.0	2.5	4.2
Aldosterone (ng/liter)	92	203	95	145	64	128
Plasma volume (ml/cm)	18.9	—	19.2	—	19.4	—

* Statistical significance at least at the $p < 0.05$ level compared with control levels.
Adapted from Muiesan et al.[24]

TABLE IV Effects of Verapamil and Nifedipine with Prolonged Treatment in Patients with Essential Hypertension

Index	Verapamil (80 mg, 3 times a day)		Verapamil (160 mg, 3 times a day)		Nifedipine (10 mg, 3 times a day)	
	Control	4 mo	Control	2 mo	Control	2 mo
Blood pressure (mm Hg)	164/106	143/95*	171/108	128/86*	168/108	149/95*
Heart rate (beats/min)	73	68	77	80	75	81
Plasma renin activity (ng/ml/hour)	1.7	2.2	2.1	1.4	1.6	2.7
Norepinephrine (pg/ml)	145	210	158	230*	203	333*

* Statistical significance at least at the $p < 0.05$ level compared with pretreatment control levels.
Adapted from Muiesan et al.[24]

resistance (from 2,690 to 2,276 dynes s cm^{-5}/m^2), associated with an insignificant increase in cardiac index (from 3.5 to 3.9 liters/min/m^2) and an unchanged heart rate. In addition, the caliber of the brachial artery was significantly increased.[27] More prolonged hemodynamic effects were not reported.

We have recently been investigating the hemodynamic effects of 2 newer calcium entry–blocking agents, diltiazem and nitrendipine, in 2 genetic forms of hypertension: clinical and experimental. In this report we shall compare our preliminary findings in patients with essential hypertension and in spontaneous hypertensive rats (SHRs) and Wistar-Kyoto normotensive rats (WKYs). SHRs are very similar to patients with essential hypertension[28] and permit an extension of our understanding of the many hemodynamic effects that we are not able to learn about in patients for practical and ethical reasons. By using 15-μm diameter microspheres for our hemodynamic studies in conscious, unanesthetized closed-chest rats, we can determine cardiac output and blood flow in every organ of the body.[30–32]

Methods

In brief, our experiment subjects WKYs and SHRs to a 3-week treatment period in a protocol similar to that which we have reported for most of the antihypertensive drugs that we use, including methyldopa,[33–35] clonidine,[35] hydralazine,[35] angiotensin converting enzyme inhibitors,[36] prazosin,[37] urapidil,[37,38] calcium entry–blocking drugs[39,40] and others.[41] We have therefore developed a standardized bioassay (a long-term hemodynamic assay) for ascertaining the comparative effects of new antihypertensive compounds. At the end of a 3-week treatment period, with the animal under light ether anesthesia, catheters were placed through the femoral artery, into the left ventricle, through the carotid artery and into the femoral vein, and then were exteriorized at the back of the neck. When the animal was fully recovered from this procedure, the microspheres were injected. Using the reference method, we determined cardiac output from the radioactive "envelope" of withdrawn arterial blood[30] and then measured radioactivity in all organs to determine the percentage distribution of cardiac output to each organ.[32] Then, by multiplying the cardiac output by the ratio of radioactive counts in any organ to the total radioactivity injected, we calculated a quantitative representation of blood flow to every organ of the body. Moreover, by recording arterial pressure directly, we were also able to calculate the changes in organ vascular resistances (compared with the WKYs, which were not given the drug). In each study, net organ weights were obtained to learn of possible changes in organ mass with therapy and to determine blood flow and vascular resistance indexes.

Our clinical studies were conducted in patients with essential hypertension. In these studies, systemic and regional hemodynamic effects of diltiazem and nitrendipine were determined using our previously reported hemodynamic methods.[42,43] In brief, all patients came to our laboratory in the morning after an overnight fast and after at least 4 weeks of no antihypertensive therapy. Polyethylene tubing was inserted into a brachial artery and antecubital vein to shoulder level for measurement of pressures, injection of dye or vasoactive agents and withdrawal of arterial blood for inscription of the dye curves. Indocyanine green dye, injected centrally and through the vein, permitted calculation of cardiac output. Renal and splanchnic blood flows were determined by injection of radioiodinated para-aminohippurate and indocyanine green dye, respectively. Hemodynamic indexes were calculated by standard methods. Plasma renin

TABLE V Effects of 3-Week Diltiazem Treatment on Organ Hemodynamics in Wistar Kyoto Rats (WKYs) and Spontaneously Hypertensive Rats (SHRs)

Organ	Organ Blood Flow		Organ Vascular Resistance	
	WKYs	SHRs	WKYs	SHRs
Skin	↓	↓	↑	No change
Skeletal muscle	No change	No change	No change	No change
Brain	No change	↑	No change	↓
Heart	↑	↓	↓	No change
Lungs	↓	↓	↑	No change
Kidneys	↓	↓	↑	No change
Splanchnic organs	No change	↓	↑	↓
Testes	No change	No change	↑	No change

TABLE VI Immediate Hemodynamic Effects of Diltiazem (intravenous) in 7 Patients with Essential Hypertension

Index	Control	Dose (mg/kg)		
		0.06	0.06	0.12
Mean arterial pressure (mm Hg)	118	107*	107*	101*
Heart rate (beats/min)	65	75*	78*	78*
Cardiac index (liter/min/m^2)	3.1	4.0	4.3	5.0
Total peripheral resistance index (U/m^2)	40	28*	26*	23*
Left ventricular ejection rate index (ml/s/m^2)	153	175*	183*	194*

* Represents statistical significance at least at the $p < 0.05$ level.

TABLE VII Preliminary Data from 7 Patients with Essential Hypertension Treated for 4 Weeks with Diltiazem (60 to 120 mg, 2 times a day)

Index	Control	Treatment
Mean arterial pressure (mm Hg)	118	107*
Heart rate (beats/min)	65	62
Cardiac index (liter/min/m^2)	3.1	3.0
Total peripheral resistance index (ml/s/m^2)	40	37*
Left ventricular ejection rate index (ml/s/m^2)	153	154
Renal blood flow (ml/min/m^2)	390	479*
Renal vascular resistance (U/m^2)	0.167	0.120*
Glomerular filtration rate (ml/min)	134	120*
Filtration fraction (%)	17.4	12.9*
Splanchnic blood flow (ml/min)	741	766
Splanchnic vascular resistance (U/m^2)	0.176	0.152

* Represents statistical significance at least at the $p < 0.05$ level.

activity, circulating norepinephrine levels and plasma volume were determined by our previously reported methods.[43] M-mode echocardiography was used to determine structural and functional cardiac changes.[7]

In all studies, rat or man, standard statistical techniques, with Student's *t* test for paired data analysis or the patient as his own control, were used.

Results

Diltiazem: *Rat studies:* When the rats were treated with diltiazem (60 mg/day by gastric tube), no systemic hemodynamic changes were observed in normotensive WKYs; however, it produced a significant fall in arterial pressure, associated with a fall in total peripheral resistance, in the SHRs. These systemic hemodynamic changes were also associated with some slowing of heart rate and reduction in cardiac index, which were not of statistical significance. There were no changes in LV mass or the weight ratio of the left ventricle to total body. We also determined changes in organ hemodynamics in these WKYs and SHRs. In the normotensive WKYs, vascular resistance increased in the skin, lungs, kidneys, splanchnic organs and testes, but decreased in the heart. In contrast, vascular resistance decreased in the brain and the splanchnic organs of the SHRs, but remained unchanged in the other organs (Table V). These findings differed somewhat from our preliminary findings in man with essential hypertension.

Clinical studies: We have obtained preliminary hemodynamic measurements in 7 patients with uncomplicated essential hypertension who first received intravenous diltiazem (0.24 mg/kg in divided doses) and were then treated with the oral formulation for 4 weeks. These 7 patients, whose age averaged 47 years, included 6 men and 1 woman. Following logarithmi-

TABLE VIII Comparison of Immediate Hemodynamic Effects of Nitrendipine in Wistar Kyoto Rats (WKYs) and Spontaneously Hypertensive Rats (SHRs) and in Patients with Essential Hypertension

	WKYs		SHRs		Essential Hypertensive Patients	
	Control	Treatment	Control	Treatment	Control	Treatment
No. of subjects	10	10	10	7	7	7
Dose	0	10 mg/kg	0	10 mg/kg	0	20 mg
Mean arterial pressure (mm Hg)	127	108*	186	141*	113	94*
Heart rate (beats/min)	366	407*	396	408	72	84*
Cardiac index (ml/min/kg)	269	280	275	268	2.9	3.4*
Total peripheral resistance index (U/kg)	0.48	0.38*	0.69	0.56*	41	29*

* Represents statistical significance at least at the $p < 0.05$ level.

TABLE IX Immediate and Prolonged Hemodynamic Effects of Nitrendipine in Wistar Kyoto Rats (WKYs) and Spontaneously Hypertensive Rats (SHRs)

	Immediate		Prolonged	
Organ	WKY	SHR	WKY	SHR
Skin	No change	↑	No change	No change
Skeletal muscle	No change	No change	↓	↓
Brain	↓	No change	No change	No change
Heart	↓	↓	No change	↓
Kidneys	↓	↓	No change	↓
Adrenals	↓	↓	—	—
Splanchnic organs	↓	No change	↓	No change

* Adapted from Sesoko et al[39] and Kobrin et al.[40]

cally incremental doses (0.06, 0.06 and 0.12 mg/kg, intravenously), arterial pressure progressively fell from 118 to 101 mm Hg within a rather short period. This was associated with a reflexive increase in heart rate, cardiac index and LV ejection rate index, as calculated total peripheral resistance declined (Table VI). When these same patients continued treatment for 4 weeks (60 to 120 mg, 2 times a day), arterial (systolic/diastolic) pressures fell from 165/95 to 149/86 mm Hg after 4 weeks. However, the reflexive increase in heart rate, cardiac index and LV ejection rate was no longer observed, while total peripheral resistance was further reduced (Table VII). Thus, after the immediate reflexive stimulation with intravenous diltiazem, more prolonged therapy evoked either some form of baroreceptor "adaptation" or lesser adrenergic stimulation of the heart.

Nitrendipine: *Rat studies:* This compound is a second generation of nifedipine. We administered the drug (20 mg/kg/day) by gastric tube to WKYs and SHRs; similar to our diltiazem experience (60 mg/kg/day), we obtained the same magnitude of reduction in pressure as we had observed with diltiazem. However, the pressure reduction was observed immediately after as well as with prolonged treatment in both the normotensive WKYs and the SHRs.[39,40] This pressure fall was associated with a significant reduction in total peripheral resistance, without a reflexive increase in cardiac index or heart rate (Table VIII). In addition, and unlike our diltiazem experience, both WKYs and SHRs demonstrated a reduced cardiac mass with 3 weeks of treatment. Thus, although the 2 calcium entry–blocking drugs had similar salutary hemodynamic effects, their effects on cardiac mass were different and were not solely related to a reduction of arterial pressure or reversal of LV hypertrophy.

Unlike diltiazem, the immediate effect of nitrendipine (after intravenous injection) on organ hemodynamics was a significant reduction in brain, heart, renal, adrenal and splanchnic vascular resistances in WKYs whereas in the SHRs there was a significant fall in vascular resistance in the heart, kidneys and adrenal glands, and a rise in cutaneous resistance.[39,40] With prolonged treatment (3 weeks) the hemodynamic changes were different from those we observed with diltiazem. Nitrendipine decreased vascular resistance in WKY skeletal muscle and the splanchnic organs, and reduced vascular resistance in skeletal muscle, heart and kidneys in the SHRs (Table IX). Thus, we must conclude that the hemodynamic effects of the calcium entry–blocking drugs on the various regional circulations differ, depending on the agent studied.

Clinical studies: We also studied the immediate hemodynamic effects of nitrendipine in 12 patients with essential hypertension after a single 20-mg oral dose.[25] This permits comparison with the immediate findings in SHRs and in our other patients after intravenous diltiazem. Only 7 of the 12 patients demonstrated an immediate fall in pressure, which was produced by a decreased total peripheral resistance and was associated with a reflex increase in heart rate, cardiac index and LV ejection rate (Table VIII) that could be related

to an increase in circulating norepinephrine levels (from 310 to 481 pg/ml).

Cardiac mass: These findings with diltiazem and nitrendipine with respect to changes in cardiac mass reflect our present lack of understanding of the mechanisms of action of antihypertensive drugs on myocardial protein synthesis. As indicated, the diuretics have little effect on cardiac mass; the vasodilating agents hydralazine and minoxidil also either have no effect or may even increase cardiac mass despite a profound and beneficial hemodynamic effect on reducing LV afterload.[35,44] In contrast, the angiotensin converting enzyme inhibitors may reduce cardiac mass in hypertensive animals[36,45] and man.[21,46] The centrally acting antihypertensive agents have varying effects: methyldopa reduces cardiac mass in normotensive and hypertensive animals[34,35,47] and in hypertensive patients,[48,49] whereas clonidine, an agent with similar pharmacologic and hemodynamic effects, does not reduce mass until high doses are used that no longer exhibit antihypertensive effects.[35]

The heterogeneous class of calcium entry–blocking agents displays varying effects on cardiac mass, and this may be related to their respective intracellular actions.[50] It is of interest that those agents that reduce cardiac mass only seem to affect protein synthesis in the heart; in each of the foregoing studies the weights of the other organs remained unaffected.[33,35,40] A variety of mechanisms has been offered as explanation for the reduction in cardiac mass; it has been variously attributed to stimulation of the renin-angiotensin system, the adrenergic nervous system or perhaps those factors that inhibit calcium entry.[4,8,40] Tissue culture studies have shown that addition of angiotensin II initiates protein synthesis;[51] and infusion of norepinephrine and other adrenergic agents in subpressor amounts also initiates ventricular hypertrophy.[52,53] It is clear that our understanding of this phenomenon is only beginning. Until we understand the molecular mechanisms involved in protein synthesis—and the fundamental mechanisms that serve to transduce the physiologic signal of pressure overload to the biochemical response of myocardial protein synthesis—this understanding will remain incomplete.

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Effects of Diltiazem on Hormonal and Hemodynamic Responses to Lower Body Negative Pressure and Tilt in Patients with Mild to Moderate Systemic Hypertension

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Mean arterial blood pressure, forearm vascular resistance, plasma norepinephrine, plasma renin activity and aldosterone responses to graded lower body negative pressure and tilt at 80° were examined in 10 men with mild to moderate essential hypertension before and after 12 weeks of diltiazem (240 to 360 mg/day) therapy. Diltiazem therapy lowered basal supine systolic and diastolic blood pressures without affecting basal heart rate. Mean arterial blood pressure and forearm vascular resistance were decreased from 114 ± 1.5 to 105 ± 1 mm Hg, $p < 0.01$ and from 29.3 ± 3.5 to 18.9 ± 2.1 units, $p < 0.01$, respectively. Diltiazem therapy had no effect on basal supine levels of norepinephrine, plasma renin activity or aldosterone, nor on the responses of these hormones to lower body negative pressure. Diltiazem did decrease the forearm vascular resistance responses to lower body negative pressure and tilt. Diltiazem abolished an orthostatic increase (10 ± 0.3 mm Hg) in mean arterial blood pressure and this was associated with a greater plasma norepinephrine response to tilt. These results suggest that diltiazem decreases vascular resistance through a reduction in the postjunctional effects of norepinephrine on vascular smooth muscle.

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Diltiazem hydrochloride, a Ca^{++} flux inhibitor, appears to lower blood pressure primarily by reducing peripheral vascular resistance.[1–4] Diltiazem and other Ca^{++} flux inhibitors exert their smooth muscle vasodilatory effects partly through interference with catecholamine-induced vasoconstriction.[5] Norepinephrine increases transmembrane Ca^{++} transport into smooth muscle, through α_1 and α_2 adrenoceptor-modulated opening of slow calcium channels, thereby causing vasoconstriction.[6,7] In addition, Ca^{++} may increase the release of catecholamines from the adrenal medulla[8] and calcium-channel blockers appear to interfere with these processes.[5,9] The effect of calcium-channel blockers on norepinephrine-induced vasconstriction is further evidenced by the observation that diltiazem attenuates the rise in blood pressure associated with norepinephrine infusion.[10,11]

Sympathetic nervous system input into the skeletal muscle vasculature plays an important role in regulating muscle blood flow.[12–15] Sympathetic nervous system input into this vascular bed is modulated by several inhibitory reflexes, including a "low pressure" cardiopulmonary baroreceptor system.[16–19] Low-level lower body negative pressure, through reduction of cardiothoracic blood volume, causes significant activation of sympathetic nervous system outflow, as evidenced by increases in forearm vascular resistance[13–19] and plasma norepinephrine levels.[19] Because low-level lower body negative pressure does not alter arterial blood pressure or heart rate,[3,14,16–19] it is apparent that changes in low pressure cardiopulmonary baroreflex activity can increase peripheral sympathetic activity and vascular resistance. Although augmentation of cardiac baroreflexes has been demonstrated in mild to moderate hypertension,[18,20] it is not known whether therapy with a Ca^{++} flux inhibitor such as diltiazem

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TABLE I Mean ± Standard Error of the Mean Systolic and Diastolic Blood Pressure (BP) and Heart Rate Responses to Lower Body Negative Pressure and Tilt (80°) in 10 Men with Mild to Moderate Hypertension Before and After 12 Weeks of Diltiazem Therapy (DT)

Measurement		Baseline	−10 mm	−20 mm	−40 mm	Tilt (80°)
Systolic BP	Pre-DT	145 ± 2.5	140 ± 3	142 ± 3	137 ± 4	147 ± 5
(mm Hg)	Post-DT	136 ± 3*	138 ± 4	139 ± 3	133 ±5	131 ±3*
Diastolic BP	Pre-DT	98 ± 1	93 ± 2	93 ± 2	96 ± 2.5	107 ± 3
(mm Hg)	Post-DT	85 ± 2**	85 ± 2	84 ± 2.5*	87 ± 2.5*	92 ± 2**
Heart rate	Pre-DT	72 ± 3	72 ± 4	71 ± 3	76 ± 3	80 ± 4
(beats/min)	Post-DT	68 ± 2	66 ± 3	66± 3	71 ± 4	82 ± 2

* $p < 0.05$; ** $p < 0.01$ for post-DT versus pre-DT.

has any effect on these augmented cardiac baroreflexes. In the present study we evaluated the effects of diltiazem therapy on hormonal and hemodynamic responses after selective activation of low pressure cardiopulmonary baroreflexes through graded lower body negative pressure and tilt.

Methods

Ten men, aged 33 to 66, with mild to moderate essential hypertension, were studied in the Hypertension Research Laboratory at the McGuire Veterans Administration Medical Center. Mean arterial blood pressure ranged from 95 to 114 mm Hg after all antihypertensive medications had been discontinued for 4 weeks. The patients had no other major medical illnesses such as coronary artery disease, congestive heart failure, renal insufficiency, chronic obstructive lung disease or diabetes mellitus. Studies were conducted before and after 12 weeks of diltiazem therapy at a dosage level of 120 to 180 mg, 2 times a day.

On study days, baseline blood sampling and hemodynamic measurements were initiated with the patients in a supine position and after having a heparin lock placed in a forearm vein of the left arm for 30 minutes. In order to selectively activate low pressure baroreceptors with lower body negative pressure, subjects were positioned in a lower body negative pressure chamber that encased them below the iliac crest. The chamber was sealed and connected to an adjustable vacuum. Graded lower body negative pressure was applied at −10, −20 and −40 mm Hg. Lower body negative pressure was maintained at each consecutive level for 5 minutes at 10-minute intervals. Forearm blood flow was measured in the right arm with a mercury-in-silastic strain gauge plethysmograph and intermittent venous occlusion technique as previously described.[21] Blood pressure was measured in the left arm by an automatic cuff method and recording device (Critikon model 1160). Forearm blood flow was calculated from the rate of increase in forearm volume during venous occlusion expressed as ml/min/100 ml forearm volume. Forearm vascular resistance was then calculated by dividing the mean arterial pressure (diastolic pressure plus one-third of the pulse pressure in mm Hg) by the forearm blood flow.

After the lower body negative pressure studies, the subjects remained supine for 30 minutes; then basal hemodynamic determinations and blood sampling were done. The subjects were then tilted at an 80° angle with the horizon and measurements were repeated after 10 minutes of tilting.

Blood samples (6 ml) were obtained before and after each level of lower body negative pressure, as well as before and after tilt for measurement of plasma catecholamines, plasma renin activity and aldosterone. Samples for catecholamines were collected in prechilled heparinized tubes and plasma was stored at −100° C until assayed. Catecholamines were assayed by high performance liquid chromatography, using electrochemical detection.[22,23] Detection in this system is coulometric and the sensitivity is less than 5 pg for norepinephrine, dopamine and epinephrine. Plasma renin activity was measured by radioimmunoassay for angiotensin I after titration to a pH of 7.4 with phosphate buffer and incubation at 37° C in the presence of angiotensinase inhibitors.[24] Sensitivity of this assay is 0.2 ng/ml/hour and intrassay coefficient of variation is 4%. Aldosterone was measured by radioimmunoassay after extraction and column separation.[24] Sensitivity for this assay is 0.4 ng/dl and the intrassay coefficient of variation is 6%. Statistical differences in levels of plasma catecholamines, plasma renin activity, aldosterone and hemodynamic parameters, as well as responses to lower body negative pressure and tilt before and after diltiazem treatment, were determined by analysis of variance. Multiple regression analysis was used to calculate correlation coefficients between various parameters, and values are significant at $p < 0.05$. Data are presented as mean ± standard error.

Results

Table I shows that diltiazem therapy decreased both resting supine systolic and diastolic blood pressures in these 10 men with mild to moderate hypertension. Mean arterial pressure was decreased ($p < 0.01$) from 114 ± 1.5 to 105 ± 1 mm Hg over the 12-week treatment period. Neither systolic nor diastolic blood pressure changed in response to graded lower body negative pressure (Fig. 1). Before diltiazem therapy, there was an increase in both systolic ($p < 0.05$) and diastolic ($p < 0.01$) blood pressure in association with tilt. After diltiazem therapy, the increase in systolic and diastolic blood pressure with tilt was eliminated. Diltiazem therapy alone had no effect on heart rate. There was no change in heart rate associated with lower body negative pressure before or after diltiazem treatment; however, heart rate increased ($p < 0.05$) with tilting both before and after diltiazem therapy.

Diltiazem therapy was associated with a decrease ($p < 0.01$) in supine basal forearm vascular resistance from 29.3 ± 3.5 to 18.9 ± 2.1 units. The reduction in basal forearm vascular resistance correlated ($r = 0.74$) with the reduction in mean arterial pressure. Forearm vascular resistance was incrementally increased from −10 through −40 mm Hg of lower body negative pressure before diltiazem (Fig. 1). The incremental responses in forearm vascular resistance to lower body negative pressure were markedly decreased ($p < 0.001$) after diltiazem therapy at all levels of graded lower body negative pressure.

There was no change in plasma dopamine, epinephrine or norepinephrine levels in response to lower body negative pressure or tilt. Before diltiazem therapy there was an increase ($p < 0.01$) in plasma norepinephrine from 132 ± 14 ng/ml to 189 ± 15 ng/ml at −10 mm Hg of lower body negative pressure and to 265 ± 55 ng/ml at −40 mm Hg of lower body negative pressure (Fig. 2). Tilting at 80° was also associated with an increase ($p < 0.01$) in plasma norepinephrine from basal supine levels. After diltiazem therapy there was no significant difference in basal supine norepinephrine levels or in norepinephrine levels after graded lower body negative pressure. However, the norepinephrine response to tilting after diltiazem therapy was greater ($p < 0.01$) than that before therapy.

Basal levels of plasma renin activity and aldosterone as well as levels after graded lower body negative pressure and tilt were similar before and after diltiazem (Fig. 3). Both plasma renin activity and aldosterone levels were increased ($p < 0.05$) after −40 mm Hg lower body negative pressure. In addition, there were plasma renin activity and aldosterone responses to tilt ($p < 0.05$) before and after diltiazem therapy.

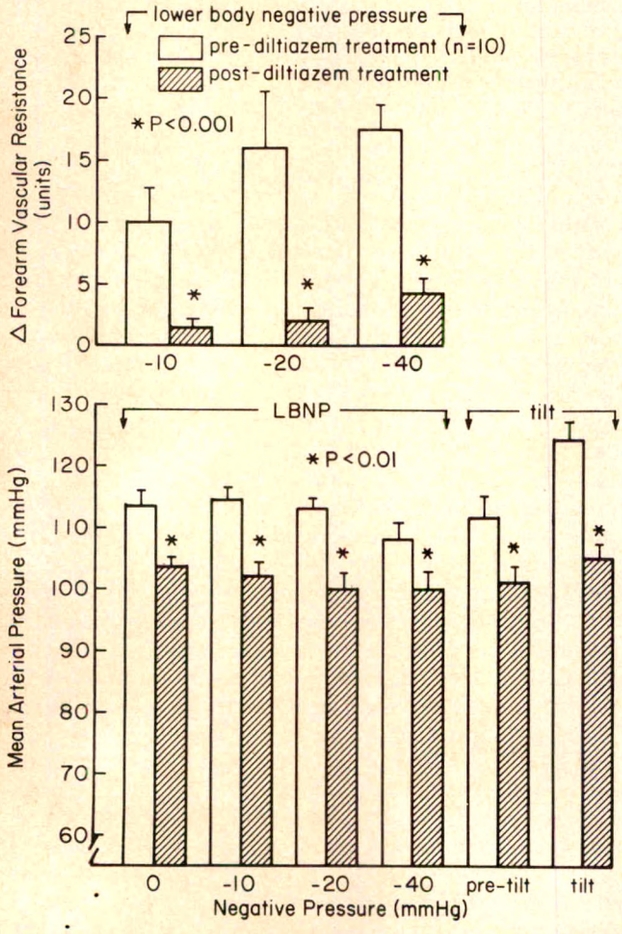

FIGURE 1. Mean ± standard error of the mean response of forearm vascular resistance and mean arterial pressure to graded lower body negative pressure in 10 men with mild to moderate essential hypertension before and after diltiazem therapy. *denotes a statistical difference between the pre-diltiazem and post-diltiazem responses.

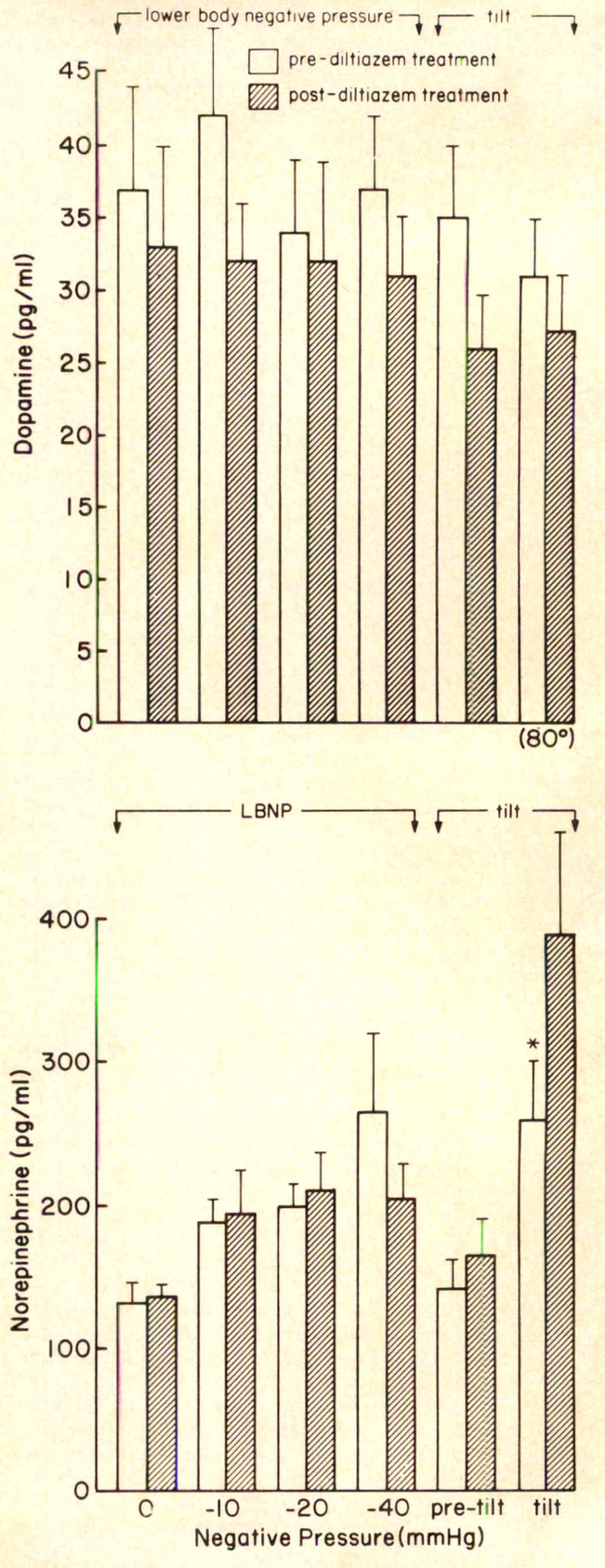

FIGURE 2. Mean ± standard error of the mean response of plasma dopamine and norepinephrine to graded lower body negative pressure in 10 men with mild to moderate essential hypertension before and after diltiazem therapy. *denotes a statistical difference between the pre-diltiazem and post-diltiazem responses.

Discussion

This study demonstrates that in patients with mild to moderate hypertension, graded lower body negative pressure unassociated with blood pressure changes results in sympathetic nervous system activation. Our observations in hypertensive subjects are thus similar to those previously observed in normotensive subjects.[19,25] Goldsmith et al[19] have observed that in normotensive subjects forearm vascular resistance during lower body negative pressure was accompanied by an increase in plasma norepinephrine. Kiowski and Julius[25] observed an increase in plasma norepinephrine during transient occlusion of venous return from the lower extremities. Our data are also consistent with those of Sundlöf and Wallin,[14] who found a consistent increase in multiunit sympathetic activity in recordings from the muscle branches of the medium nerve after lower body negative pressure in normotensive subjects.

Thus, unloading of low pressure cardiopulmonary mechanoreceptors, without associated changes in sinoaortic baroreceptor activity, results in heightened activity of the sympathetic nervous system. The mechanism of increased plasma norepinephrine levels is probably via decreased input from cardiopulmonary receptors with vagal afferents, deactivation of which in animals leads to increased sympathetic activity.[26]

After tilt there was also an increase in plasma norepinephrine that was seen in association with lower body negative pressure. This observation concurs with the results of previous studies[27–29] that have established the importance of sympathetic nervous system activation, and increases in plasma norepinephrine levels, in maintenance of blood pressure, especially in response to posture changes. The sympathetic activity response to tilt appears to be mediated primarily through activation of sinoaortic baroreceptors and afferent pathways, which inhibit the same neuronal pools of the vasomotor center as does afferent input from cardiopulmonary receptors.[30,31] A lack of epinephrine and dopamine response to graded lower body negative pressure and upright tilt suggests that, in contrast to peripheral sympathetic release of norepinephrine, adrenal medullary release of catecholamines is not mediated by cardiopulmonary sinoaortic baroreflexes.

In vitro studies have shown that the release of catecholamines from the adrenal medulla in response to a variety of secretogogues is calcium-dependent.[32,33] Norepinephrine release from noradrenergic neurons is also calcium-dependent because the transport of secretory granules to the cell surface, fusion of the granules with surface membrane and subsequent exocytosis utilize a contractile process that is regulated by calcium and cyclic nucleotides.[34] In vitro studies showed that diltiazem, presumably through its Ca^{++} flux inhibitory action, reduced adrenal medullary catecholamine release in response to several secretagogues.[34] In contrast to in vitro evidence that diltiazem might decrease catecholamine secretion, Inonye et al[35] reported that diltiazem therapy increased plasma norepinephrine and plasma renin activity levels in hypertensive patients. Our findings—that diltiazem therapy had no effect on basal supine levels of norepinephrine, epinephrine or dopamine—are in agreement with another recent report of no change in plasma norepinephrine or epinephrine after diltiazem therapy in normotensive subjects.[11] Further, we observed no effect of diltiazem on plasma norepinephrine responses to graded lower body negative pressure. Diltiazem therapy was associated with an enhanced plasma norepinephrine response to tilt, probably related to a baroreceptor-modulated increase in efferent sympathetic traffic owing to a lower post-diltiazem blood pressure after tilt.

There was a strong correlation between the decrease in forearm vascular resistance and the decrease in ar-

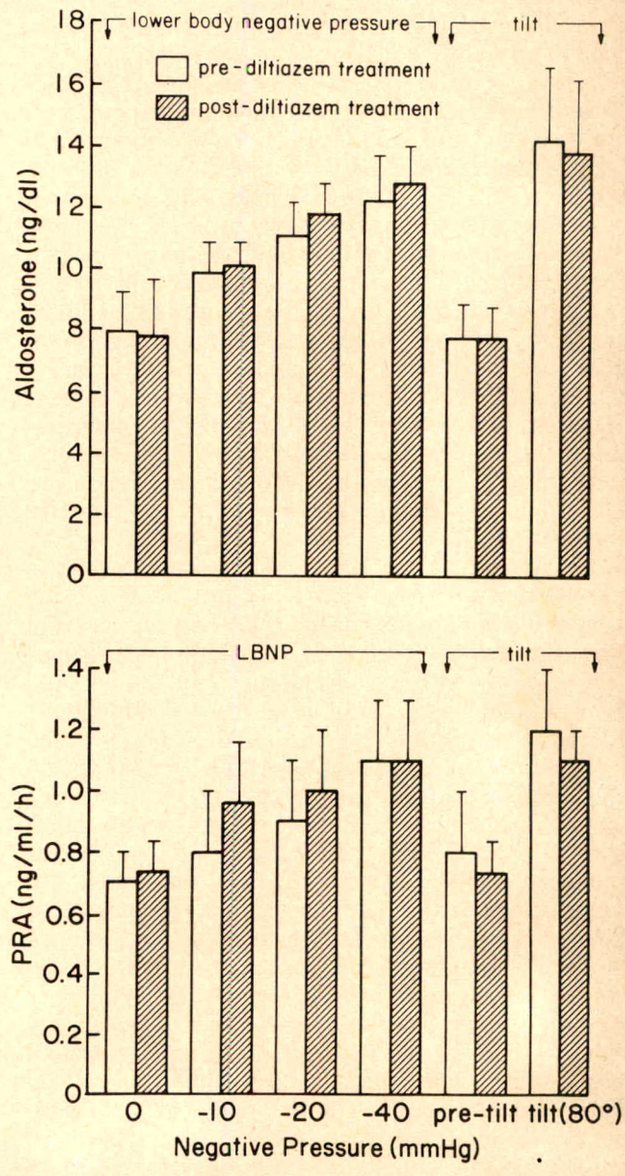

FIGURE 3. Mean ± standard error of the mean response of plasma renin activity (PRA) and aldosterone to graded lower body negative pressure in 10 men with mild to moderate essential hypertension before and after diltiazem therapy. *denotes a statistical difference between the pre-diltiazem and post-diltiazem responses.

terial blood pressure in our patients with mild to moderate hypertension. Diltiazem therapy inhibited the vascular reactivity response to lower body negative pressure without affecting the plasma norepinephrine response. These observations suggest that the effects of diltiazem in reducing blood pressure are due to a reduction in the postjunctional action of norepinephrine on vascular smooth muscle contractility. These observations are consistent with the idea that the sympathetic nervous system affects intracellular calcium levels by opening slow calcium channels, an effect modulated through α_1 and α_2 adrenoceptors.[6,7] It has been previously observed that calcium levels in human platelets are elevated in hypertensive subjects.[7] It has also been observed that, in clinical settings, the increased intracellular free calcium levels can be decreased by calcium antagonists and the decrease in intracellular calcium relates directly to the decrease in blood pressure.[36]

There is considerable in vitro evidence that Ca^{++} has significant effects on renin and aldosterone secretion.[37–39] Ca^{++} flux inhibitors have been reported to increase plasma renin activity[37] and decrease aldosterone[39] secretory responses to various secretogogues. In the clinical setting, diltiazem therapy has been reported to increase plasma renin activity acutely in normotensive subjects[11] and after long-term therapy in hypertensive subjects.[35] Our observations—that diltiazem therapy did not affect basal supine plasma renin activity or lower body negative pressure and tilt-related increase in plasma renin activity—are in agreement with those of Aoki et al[40] in normotensive and hypertensive subjects. In the present study, diltiazem therapy had no effect on plasma aldosterone levels or on aldosterone responses to graded lower body negative pressure and tilt.

This is the first report of a renin and aldosterone response to lower body negative pressure and to tilting in patients with hypertension. Our observation of a renin response to lower body negative pressure supports prior observations of plasma renin responses to venous pooling of blood in legs caused by thigh cuff inflation[25] and lower body negative pressure.[41] The increase in renin release that occurs with assumption of the upright posture probably results from the reflex increase in sympathetic activity induced by the blood volume shift to the lower limbs.[42–44] The basis for this conclusion is the absence of any postural increase in renin during head-up tilt in animals with denervated kidneys[42] and in normal subjects after β-adrenergic blockade[44] or under the influence of antigravity devices.[43] The finding of a renin response to lower body negative pressure in this study provides additional evidence that the cardiopulmonary receptor system plays an important role in modulating renin release in response to vascular fluid shifts. Aldosterone responses to lower body negative pressure and tilt probably occur secondary to activation of renal renin release.

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Rationale for Calcium Entry–Blocking Drugs in Systemic Hypertension Complicated by Coronary Artery Disease

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There is considerable rationale for the use of the calcium entry–blocking drugs for the treatment of hypertension and prevention of recurrent episodes of angina pectoris in patients with systemic hypertension and significant coronary artery disease—the 2 entities commonly occurring together. Calcium entry–blocking drugs improve myocardial blood flow while decreasing myocardial oxygen demand. These agents can be given to most patients with ischemic heart disease and its complications, and are associated with a relatively low incidence of serious adverse effects and toxicity during long-term therapy. They reduce the frequency of anginal attacks, prolong exercise time to ST-segment depression or angina and improve exercise capacity. With long-term therapy, tolerance does not develop as it does in many patients with the "long-acting" nitrates.

Calcium entry–blocking drugs reduce systolic blood pressure in patients with hypertension by a decrease in peripheral vascular resistance and a uniform improvement in blood flow affecting the myocardium, kidney and brain. There are no central nervous system adverse effects and hypokalemia does not occur. Unlike therapy with the β-blocking drugs, chronic treatment with the calcium entry blockers does not reduce the serum level of high-density lipoprotein cholesterol nor increase serum triglyceride concentration. The calcium blockers decrease the arterial blood pressure without increasing intravascular plasma volume and are associated with only a slight increase in reflex-mediated sympathetic activity and heart rate, the latter occurring predominantly with nifedipine.

Calcium entry–blocking drugs provide alternative or preferred therapy to β-blocking agents in patients with a combination of hypertension and angina pectoris. They are likely to be more effective in elderly patients and in blacks and can be prescribed for patients with bronchospastic disease and symptomatic peripheral vascular disease. For many reasons, of the 3 currently available calcium blockers, diltiazem is likely to be the most effective calcium entry blocker for monotherapy in patients with hypertension and ischemic heart disease, although most worldwide experience for this indication has been with nifedipine.

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Systemic hypertension and ischemic heart disease frequently occur in the same patient for several reasons. First, hypertension is a well-known risk factor for coronary atherosclerosis and effective treatment of hypertension reduces the morbidity and mortality resulting from coronary artery disease (CAD), as well as from stroke. Second, several of the diseases or conditions associated with 1 of these 2 common disorders are also independently associated with the other. For example, systemic hypertension often results from chronic renal disease and uremia accelerates coronary atherosclerosis. Also, an increased incidence of both hypertension and symptomatic coronary atherosclerosis is found in patients with obesity, diabetes mellitus or a long history of cigarette smoking. Finally, in patients with severe coronary atherosclerosis and in those with mild to moderate CAD but considerable left ventricular (LV) hypertrophy, hypertension is an important determinant of an increased myocardial oxygen demand. The severity of angina is often reduced in such patients when the systolic blood pressure is lowered by appropriate drug therapy; in many patients anginal episodes actually disappear when the blood pressure is controlled by medical therapy.

Accordingly, many patients with both hypertension and symptomatic CAD will require medical therapy with drugs selected both for their efficacy as antianginal agents and for their ability to reduce the arterial blood pressure at rest and during exercise. This article will focus first on the use of calcium entry–blocking

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drugs as antianginal agents and then on the utility of these drugs for the treatment of hypertension complicated by ischemic heart disease.

Calcium Entry Blockers as Antianginal Agents

The desirable characteristics of an antianginal agent are listed in Table I. Each of the currently available calcium entry–blocking drugs—diltiazem, nifedipine and verapamil—has been shown to reduce angina due to coronary artery spasm (variant angina) and to prevent, attenuate or reverse the angiographically demonstrated coronary artery spasm that can be produced in susceptible patients with intravenous ergonovine stimulation.[1–7] Each of these drugs has also been shown to decrease the frequency of angina attacks and to improve exercise tolerance in patients with chronic stable angina.[8–18] During treadmill or bicycle exercise, diltiazem, nifedipine and verapamil increase the exercise time to ST-segment depression (as measured by electrocardiogram monitoring) and prolong the time to the development of angina as well as the total exercise duration. Several studies[19–21] indicate that calcium blockers are as efficacious as β-blocking drugs or "long-acting" nitrates in preventing recurrences of myocardial ischemia in patients with unstable angina, most of whom have angina at rest. In 1 study,[21] nifedipine was particularly effective in the subgroup of patients who tended to show ST-segment elevation on the electrocardiogram during episodes of ischemic chest pain. It is likely that an element of increased coronary vasomotor tone (coronary artery spasm) contributes to myocardial ischemia in many such patients.[22–24]

Although controversy exists as to the primary mechanism, calcium entry blockers probably exert their salutary effects in patients with variant angina, angina at rest and chronic exertional angina by both reducing myocardial oxygen demand and improving coronary blood flow (Fig. 1). The calcium entry–blocking drugs reduce the heart rate-blood pressure product at rest and during exercise: nifedipine decreases arterial blood pressure during exercise, while verapamil and diltiazem reduce heart rate during exercise. Thus, these drugs favorably affect several factors that influence myocardial oxygen demand. Also, calcium blocking drugs cause coronary artery and systemic arterial dilatation and may reverse, blunt or prevent coronary artery vasoconstriction. Therefore, calcium blockers provide effective therapy for patients with variant angina due to coronary artery spasm and may reverse any coronary vasoconstriction in otherwise normal coronary arteries or in the lumen of areas with eccentric coronary artery stenosis; in either case coronary blood flow is improved to areas of myocardial ischemia in patients with chronic exertional angina or unstable angina.

Therapy with a calcium entry blocker is applicable to most patients with ischemic heart disease and its complications. This heterogeneous group of drugs does not produce or worsen symptoms in patients with bronchospastic lung disease or peripheral vascular disease. They can also be given to patients with diabetes mellitus, including those taking insulin. However, they should not be used in patients with severe hypotension or overt congestive heart failure. The differences in potency for various therapeutic actions are useful when administering calcium entry blockers in patients with complications resulting from ischemic heart disease. For example, nifedipine can be used for the treatment of angina in patients with resting bradycardia and first degree atrioventricular (AV) block because it does not produce the same depression of AV conduction and sinoatrial nodal activity in therapeutic doses that occurs with verapamil and to a lesser extent with diltiazem. In patients with severe LV dysfunction who are not in overt heart failure, diltiazem, the calcium blocker with the least depressant effect on LV performance, can be used to treat angina, whereas verapamil in particular is more likely to produce or exacerbate any symptoms of heart failure.

TABLE I Desirable Characteristics of Antianginal Drugs

Improvement of coronary blood flow while decreasing myocardial oxygen demand
Applicability to most patients with ischemic heart disease and its complications
Relatively low incidence of adverse effects and toxicity during long-term therapy
No development of tolerance during long-term treatment
Favorable modification of risk factors for progressive coronary atherosclerosis

Adverse effects occur with the calcium entry blockers, but most of these reactions are relatively minor and unassociated with an increase in either morbidity or mortality; true drug toxicity is uncommon. The incidence of adverse effects is by far the greatest with nifedipine because of its marked strong arterial vasodilator effects in therapeutic doses and the resulting reflex increase in sympathetic activity. Dizziness, cutaneous flushing and marked postural hypertension are particularly common adverse effects seen with it. Constipation is most common with verapamil, and all 3 cause peripheral edema, frequently transient in nature. Diltiazem is associated with a relatively small incidence of adverse effects but with all 3 drugs, untoward effects are more common at high doses. The development of advanced AV block or se-

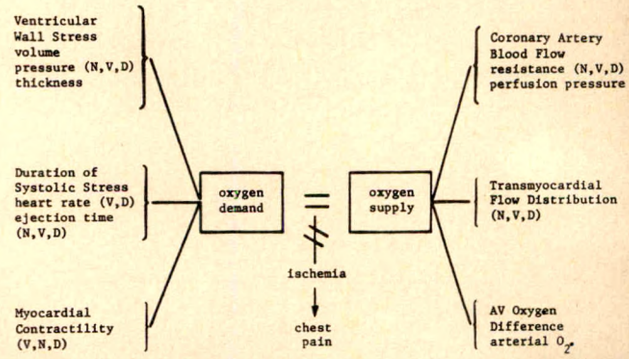

FIGURE 1. Favorable effects of currently available calcium entry–blocking drugs on the determinates of myocardial oxygen demand and coronary blood flow. N, V and D = nifedipine, verapamil and diltiazem, respectively, in order of relative potency.

vere heart failure with the use of these drugs is uncommon if patients who have preexisting first degree AV block, peripheral conduction abnormalities or evidence of heart failure before therapy are excluded. These complications occur more commonly when a calcium entry blocker is combined with a β-blocking drug, particularly when the calcium blocking drug is verapamil. Interestingly, the calcium entry–blocking drugs when used alone have been shown to actually improve the LV ejection fraction and the response of the LV ejection fraction to exercise in patients in whom myocardial ischemia is improved. Calcium entry blockers can also affect LV performance by arterial vasodilatation, which reduces afterload and improves the LV ejection fraction, despite the direct negative inotropic effect (Fig. 2).[12,15]

Neither tachyphylaxis nor partial tolerance appears to develop to the antianginal effects of the calcium entry blockers. Petru et al[25] have demonstrated the same antianginal efficacy of diltiazem in patients with chronic exertional angina 16 months after the initiation of therapy that was present at the end of 2 weeks of treatment (Fig. 3). Similar data indicate that verapamil and probably nifedipine also provide effective long-term therapy for chronic stable angina.[26]

Calcium entry–blocking drugs decrease peripheral vascular resistance and by lowering the blood pressure in patients with hypertension are effective in reducing this risk factor for coronary atherosclerosis. These agents do not adversely affect serum lipids. They do not reduce the serum level of high-density lipoprotein cholesterol or increase the serum triglyceride concentration, which often occurs in patients receiving long-term therapy with either β blockers or thiazide diuretics.

Comparison with Other Antianginal Drugs

The calcium entry–blocking drugs provide alternative or additional therapy to nitrates for variant or unstable angina as well as alternative or additional therapy to nitrates or β-blocking drugs for chronic stable angina. The nitrates act primarily by reducing venous return, LV volume and arterial pressure, thus decreasing LV wall stress, a major determinant of myocardial oxygen demand at rest and during exercise.[27] In addition, they reverse any coronary vasoconstriction in the large coronary arteries or that involves the lumen in areas with eccentric coronary artery stenosis, thereby promoting improved coronary blood flow to areas of myocardial ischemia.[28] There is also some evidence that nitroglycerin improves collateral coronary blood flow in patients with severe coronary artery stenosis.[27]

There are several advantages to using nitrate therapy in patients with angina pectoris. First, there is considerable clinical experience with them, and their efficacy is well proven. This is particularly true with regard to the use of short-acting nitrates to interrupt episodes of angina pectoris. Second, the nitrates, like the calcium entry blockers, prevent and may reverse any element of coronary artery vasoconstriction contributing to episodes of myocardial ischemia. Third, nitrates frequently improve LV performance by reducing LV end-diastolic volume and thus pulmonary venous pressure. They also may improve the LV ejection fraction by afterload reduction. Fourth, the adverse effects of nitrate therapy are well defined and

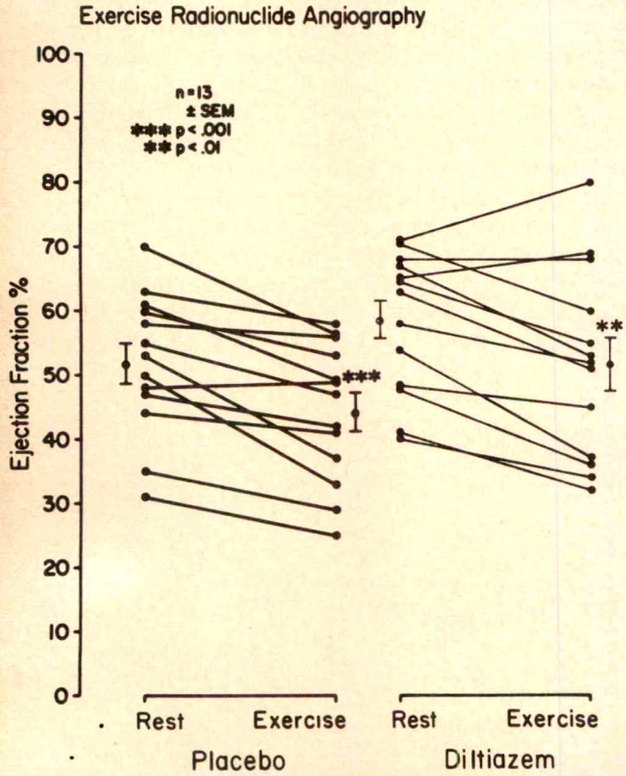

FIGURE 2. Radionuclide-determined left ventricular ejection fraction at rest and during exercise on placebo, **left,** and diltiazem, **right,** in 13 patients with chronic stable angina. SEM = standard error of the mean. Reproduced with permission from Circulation.[15]

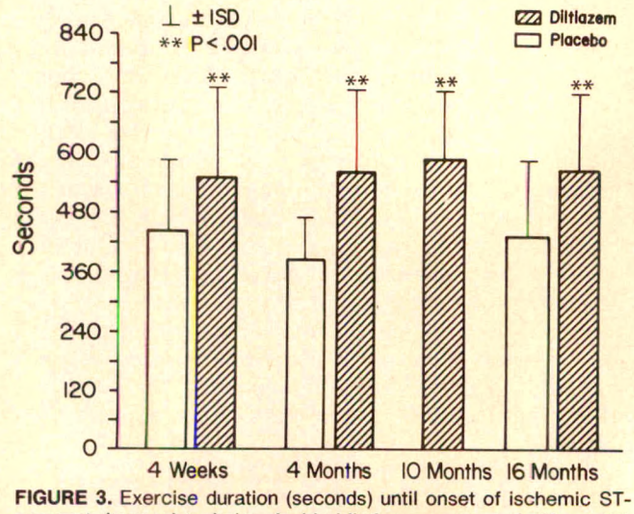

FIGURE 3. Exercise duration (seconds) until onset of ischemic ST-segment depression during double-blind crossover study (4 weeks) and during long-term follow-up at 4, 10 and 16 months in 8 patients who completed the long-term study. Values are for each diltiazem-treatment week versus all comparable placebo-treatment weeks. SD = standard deviation. Reproduced with permission from Am Heart J.[25]

there is minimal interaction with other drugs, except for the potentially additive hypotensive effect that may occur when nitrates are added to other vasodilator drugs. Finally, nitrate therapy is relatively inexpensive compared with other antianginal drugs.

There are, however, several limitations to nitrate therapy. First, currently available preparations have not been proven to provide effective once-daily or even twice-a-day therapy. This is also the case with calcium entry blockers. Importantly, partial to complete tolerance often develops in patients with angina pectoris. The duration of the reduction in arterial blood pressure and the increase in exercise tolerance after each dose lasts for a shorter duration during chronic nitrate therapy compared with the salutary effect observed early after the initiation of treatment.[29] Tolerance does not occur with the long-term use of a calcium entry blocker. Third, there are few discrete quantitative endpoints for dosage adjustments with nitrate therapy. Adverse effects are relatively common with nitrate therapy, and a reduction in the arterial diastolic blood pressure to below 60 mm Hg can often reduce coronary blood flow to areas of coronary artery stenosis that are already dilated due to local hypoxia and are "pressure dependent" for adequate perfusion.

The β-blocking drugs produce their salutary effects primarily by decreasing several determinants of myocardial oxygen demand at rest and particularly during exercise in patients with angina pectoris.[30–32] The primary effect of the β blockers is to attenuate the heart rate response to endogenous catecholamines during exercise or other forms of stress. The decrease in systemic arterial pressure at rest, and to a greater extent during exercise, is a lesser factor except in patients with systemic hypertension. The slight reduction in myocardial contractility produced by the β blockers is a relatively minor factor in reducing the myocardial oxygen demand, as is also the case with calcium blockers. The β-blocking drugs have little effect on the coronary blood supply to ischemic myocardium although a redistribution of blood flow to the subendocardial area has been demonstrated in experimental animals. In contrast, the calcium entry blockers cause coronary artery dilatation.

There are several advantages to the use of β-blocking drugs in the treatment of patients with chronic stable angina, and their beneficial effect has been well demonstrated. First, a decrease in myocardial oxygen demand at rest and during exercise has been clearly defined as the mechanism of action, and the heart rate response to exercise can be used as a therapeutic endpoint for therapy. Second, the potentially adverse effects of β blockers and their interactions with other drugs are well known. Third, specific drugs are available with sufficiently long half-lives for once-a-day therapy, which improves patient compliance. Finally, partial tolerance and tachyphylaxis, such as occur with nitrates, seldom result from β-blocker therapy.

However, there are several contraindications to the use of β-blocking drugs that modify or prevent their use in many patients. These include overt congestive heart failure, advanced AV block and documented sinoatrial nodal disease. Because all β-blocking drugs, including the "cardioselective" ones, affect both β_1 and β_2 receptors when given in moderate to high dosages, β-blocking drugs often worsen symptoms in patients with bronchospastic disease or symptomatic peripheral arterial disease. By contrast, no exacerbation of symptoms occurs with the calcium entry blockers. Also, β-blocking drugs tend to increase serum triglyceride levels and reduce the serum level of high-density lipoprotein cholesterol, thus worsening lipid abnormalities that are often present in patients with ischemic heart disease and for whom they are a risk factor. Calcium entry–blocking drugs produce no change in serum lipid levels.

Several clinical studies have been performed comparing 1 or more calcium entry–blocking drugs with a β blocker, usually propranolol, or with a "long-acting" nitrate, usually isosorbide dinitrate, in patients with chronic stable angina.[10,11,18,32–37] In general, the calcium entry blockers appear to be equally or possibly more effective in the treatment of patients with angina pectoris, depending on the patient population studied and the doses used. "Step-therapy" for angina pectoris is now popular, and many physicians prescribe 1 antianginal drug initially and then add a second and subsequently a third medication for patients with an unsatisfactory reduction in the frequency of anginal attacks. However, no formula for using a particular sequence of drug therapy (for example, "long-acting" nitrate, then β blocker, then calcium blocker) has been proven better than another (for example, calcium or β blocker first, then a nitrate, then 1 of the remaining group of drugs).

Combined therapy with a calcium entry–blocking drug and a β-blocking agent or a "long-acting" nitrate produces a greater salutary result than single drug therapy in some patients with chronic stable angina. In certain patients, "triple therapy" for angina (calcium blocker plus β blocker plus nitrate) provides an even greater reduction in the frequency of angina and improves exercise tolerance more than with monotherapy. However, adverse effects are likely to be more common in combined therapy and deleterious results may occur. When calcium entry–blocking drugs and nitrates are combined, the reduction in systemic vascular resistance is additive and severe postural hypotension results in some patients. Accordingly, the dosage of 1 vasodilator often must be reduced when the second agent is added, and careful measurement of the supine and upright blood pressure before and after therapy is important.

Both β and calcium entry blockers decrease sinoatrial nodal activity, prolong AV conduction and depress LV performance. Accordingly, combination therapy with drugs from these 2 groups is likely to produce marked bradycardia, advanced AV block or LV failure in certain patients, particularly when verapamil is the calcium entry blocker. Verapamil has the greatest depressant effect on sinoatrial nodal activity, AV conduction and LV performance.[38–41] However, such complications appear to be infrequent and are unlikely to occur in patients who have no manifestations of sino-

TABLE II Additional Desirable Characteristics of Antianginal, Antihypertensive Drugs

Decrease in total peripheral resistance
Efficacy in elderly patients
No expansion of intravascular (plasma) volume
Minimal reflex cardiac stimulation
Once- or twice-a-day dosage
Relatively low cost for effective therapy

atrial nodal disease, AV block or congestive heart failure before the initiation of combined antianginal therapy.

Use of Calcium Entry–Blocking Drugs for Patients with Concomitant Hypertension in Ischemic Heart Disease

Additional characteristics that would be desirable in an antianginal drug used to treat concomitant systemic hypertension are listed in Table II. The calcium entry–blocking drugs have been used for several years in Europe for this purpose and are being used with increased frequency as monotherapy for patients with a combination of hypertension and recurrent episodes of angina pectoris.[42–47]

The ideal antihypertensive and antianginal drug should reduce arterial pressure primarily by decreasing total peripheral resistance with a relatively uniform decline in vascular resistances in the major organ circulations of the body, including the kidney, heart and brain. The calcium entry–blocking drugs possess this characteristic and increase coronary blood flow through coronary artery dilatation while decreasing the systemic blood pressure—a major determinant of LV wall stress—and thus myocardial oxygen demand. Because angina in patients with hypertension occurs more frequently with increasing age, an ideal antihypertensive and antianginal drug would be one that is proven effective in elderly patients and in blacks as well as whites. The efficacy of calcium entry–blocking drugs is not dependent on the status of the renin-angiotensin-aldosterone system; they are effective antihypertensive agents regardless of renin levels. Patients with a combination of hypertension and ischemic heart disease frequently have depressed LV performance and often develop signs and symptoms of left-sided heart failure. Therefore, in such patients it would seem appropriate to use antihypertensive, antianginal drugs that reduce peripheral vascular resistance and thus promote forward blood flow without expanding the intravascular (plasma) volume, the latter being a potentially deleterious effect of many antihypertensive drugs.[48–50] In the studies by Olivari et al[42] calcium entry–blocking drugs produced no intravascular volume expansion, no alteration in glomerular filtration rate and no change in plasma renin activity in a group of hypertensive patients in whom blood pressure was importantly reduced. Muiesan et al[45] found similar results in groups of hypertensive patients treated with nifedipine or verapamil.

Myocardial oxygen consumption is directly related to heart rate, and it is desirable to avoid tachycardia in patients with angina pectoris, because of potential myocardial ischemia. It would be desirable to use drugs for the treatment of combined hypertension and angina pectoris that produce minimal reflex stimulation of the sympathetic nervous system. The reduction in blood pressure produced by the calcium entry–blocking drugs elicits a baroreceptor reflex-mediated indirect increase in heart rate that is more commonly observed with nifedipine than with either verapamil or diltiazem. The latter 2 calcium entry blockers have a greater direct depressant effect on sinoatrial nodal activity in therapeutic doses than does nifedipine. Klein et al[44] showed that both diltiazem and nifedipine were effective in controlling mild to moderate chronic essential hypertension. The average heart rate during therapy was not significantly increased by nifedipine and was lowered by diltiazem. Nifedipine therapy was associated with a reflex activation of the sympathetic nervous system in all patients and resulted in an increase in plasma norepinephrine concentration and tachycardia in some. Moreover, diltiazem has the advantage of lowering blood pressure, reducing afterload and increasing stroke volume with a less pronounced increase in catecholamines and without reflex tachycardia. Further, adverse effects with diltiazem were uncommon and long-term therapy was well tolerated.

It would be useful to have a therapeutic agent for monotherapy in patients with hypertension complicated by ischemic heart disease that would provide effective therapy when given once or twice a day. Currently, calcium entry blockers are not available in a preparation that permits once- or twice-a-day dosing. However, new formulations of the currently available drugs that permit twice-a-day therapy are being used in clinical research studies, and other calcium entry–blocking drugs with longer half-lives should be available soon. At this time, the daily cost of therapy with calcium entry blockers is higher than either β blockers or many of the other antihypertensive drugs. The single exception is the angiotensin-converting enzyme inhibitor, captopril.

Considering the various hemodynamic effects of the 3 currently available calcium entry blockers, diltiazem will most likely become the most effective agent for monotherapy in patients with both hypertension and angina pectoris. It has fewer untoward effects than either nifedipine or verapamil, and it produces the least depression of LV performance and rarely causes reflex tachycardia. Verapamil is more likely to cause or exacerbate LV dysfunction or bradycardia, and nifedipine has the highest incidence of adverse effects, often producing reflex tachycardia.

Comparison with Other Antianginal-Antihypertensive Drugs

The β-adrenergic receptor–blocking drugs have both antianginal and antihypertensive effects. They have been used effectively as monotherapy or combined with other antihypertensive drugs in the treat-

ment of patients with both angina pectoris and hypertension. There are β-blocking drugs available for once- or twice-a-day therapy in patients with hypertension and ischemic heart disease. However, the β-blocking drugs are frequently ineffective in controlling blood pressure in blacks and in elderly patients. Calcium entry–blocking drugs may be better for this purpose. Also, the β-blocking drugs do not decrease total peripheral vascular resistance and their use is often associated with central nervous system untoward effects. In addition, the β-blocking drugs may exacerbate bronchospasm in patients with chronic lung disease or intermittent claudication in patients with generalized atherosclerosis. Finally, long-term therapy with β-blocking drugs tends to result in an increase in serum triglyceride levels while reducing levels of high-density lipoprotein cholesterol. Calcium entry–blocking drugs do not have this potentially adverse effect.

Diuretics are frequently used as first-step therapy for patients with systemic hypertension, including those with coincident CAD. It is now recognized that hypokalemia, serious arrhythmias and sudden death are potential complications of diuretic therapy in patients with systemic hypertension, particularly in those with severe coronary atherosclerosis. In addition, long-term administration of thiazide diuretics often produces the abnormal lipid profile seen with β-blocking drug therapy.

Other antihypertensive drugs that are primary vasodilators do not exert a favorable effect on blood flow to ischemic myocardium and may even precipitate angina pectoris by either causing reflex tachycardia (e.g., hydralazine) or by reducing the perfusion pressure to myocardium distal to severe coronary artery stenoses without augmenting coronary blood flow. Whether coronary artery "steal" is produced frequently by calcium entry–blocking drugs is a subject of current investigation.

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Comparison of Diltiazem and Nifedipine for Both Angina Pectoris and Systemic Hypertension

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In a randomized, double-blind, placebo-controlled crossover trial, diltiazem and nifedipine were compared in 10 patients with stable angina pectoris and mild to moderate hypertension (supine diastolic blood pressure ≥90 mm Hg). Patients received placebo for 2 weeks, then increasing doses of diltiazem (90 to 360 mg/day) or nifedipine (30 to 120 mg/day) in 3 daily divided doses over 2 weeks, followed by 1 week of therapy at the maximal dose, a 1-week placebo "washout," then crossover to the other drug. Heart rate and blood pressure at rest and during exercise, anginal frequency, nitroglycerin consumption and treadmill exercise tolerance were assessed.

Compared with placebo, anginal frequency and nitroglycerin consumption were reduced with both diltiazem and nifedipine ($p < 0.01$) and exercise tolerance was increased with both drugs ($p < 0.01$). Standing blood pressure at rest was reduced by diltiazem and nifedipine (146.6 ± 11.4/97.7 ± 5.3 mm Hg at placebo, baseline reduced to 129.6 ± 15.2/79.5 ± 13.7 mm Hg with diltiazem, and to 122.2 ± 9.9/82.0 ± 7.1 with nifedipine, $p < 0.01$ for both). Compared with placebo, diltiazem and nifedipine also reduced exercise diastolic blood pressure ($p < 0.01$), but not systolic blood pressure. Diltiazem lowered the heart rate at rest from 88.5 ± 14.4 beats/min at placebo baseline to 79.7 ± 17.9 beats/min ($p < 0.01$); the heart rate with diltiazem was 11 beats/min lower than that with nifedipine ($p < 0.05$). Both diltiazem and nifedipine had similar effects on the heart rate-blood pressure product at rest and during exercise. Both drugs were well tolerated. Thus, diltiazem and nifedipine appear equally effective and safe in patients with both hypertension and angina pectoris by relieving angina, improving exercise tolerance and reducing elevated blood pressure.

(Am J Cardiol 1985;56:41H–46H)

Systemic hypertension and coronary artery disease (CAD) are common disorders; it is therefore not unexpected that the prevalence of both conditions together is high. The incidence of these disorders concomitantly is further increased by the fact that hypertension is an important risk factor for CAD. Thus, single agents that are capable of treating both disorders, allowing for improved patient compliance, are of particular interest. To date, the therapeutic agents of choice in the management of patients with both systemic hypertension and angina pectoris have been the β-adrenergic–blocking drugs.[1] In a prior placebo-controlled, double-blind study, verapamil was shown to be a safe and effective alternative to propranolol in treating such patients.[2] Because diltiazem and nifedipine have also been shown to be effective in each condition when they occur separately,[3–10] an evaluation of their efficacy in patients with both conditions was in order. We now report the findings of a placebo-controlled, double-blind, randomized, crossover trial comparing the antihypertensive and antianginal effects of diltiazem and nifedipine in a group of patients with both stable angina pectoris and systemic hypertension.

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Methods

Patient selection: Ten ambulatory patients (7 men and 3 women) with stable angina pectoris and mild to moderate systemic hypertension were entered into the study after written and informed consent was obtained. The patients represented a subgroup from a larger study population with angina pectoris. The mean patient age was 55.7 years (range 44 to 69). The diagnosis of angina pectoris was established by: (1) clinical history of classic stable angina pectoris characterized by the occurrence of precordial chest pain, pres-

TABLE I Effects of Placebo, Nifedipine and Diltiazem on Heart Rate (HR) and Blood Pressure (BP) at Rest in Patients with Angina Pectoris and Hypertension

	Baseline (Placebo)	Nifedipine	Diltiazem	Statistical Significance: Placebo vs Nifedipine	Statistical Significance: Placebo vs Diltiazem	Statistical Significance: Nifedipine vs Diltiazem
Three-minute standing HR (beats/min)	88.5 ± 14.4	90.9 ± 17.9	79.7 ± 17.9	NS	p <0.01	p <0.05
Systolic BP (mm Hg)	146.6 ± 11.4	122.2 ± 9.9	129.6 ± 15.2	p <0.001	p <0.01	NS
Diastolic BP (mm Hg)	97.7 ± 5.3	82.0 ± 7.1	79.5 ± 13.7	p <0.001	p <0.001	NS
Rate-pressure product (beats/min × mm Hg × 10^2)	129.8 ± 22.1	111.3 ± 24.2	104.3 ± 30.4	p <0.01	p<0.01	NS

NS = not significant.

sure or distress (which had been stable for at least 3 months), usually precipitated by exercise or emotional stress and relieved by sublingual nitroglycerin, rest or removal of emotional stress, (2) demonstration of a positive ischemic response on 2 occasions to a standardized, multistage treadmill exercise test, defined as anginal pain or at least 1 mm of flat or downward-sloping ST-segment depression, 0.08 seconds after the J point or (3) both 1 and 2.

The diagnosis of CAD was made on the basis of at least 1 of the following: coronary angiography (75% luminal narrowing of at least 1 major coronary vessel) in 6 patients, and previous myocardial infarction in 6 patients. No patient had had coronary artery bypass surgery. Systemic hypertension was documented in all patients by history and by a 3-minute supine diastolic blood pressure (using Korotkoff phase V) >90 mm Hg at the end of the placebo run-in period.

Experimental design: During the study, patients were permitted sublingual nitroglycerin tablets (0.6 mg) as the only antianginal medication other than the test drugs. Nitroglycerin tablets were used as needed to treat anginal episodes and were not used prophylactically. Digitalis, propranolol, long-acting nitrates and antiarrhythmic drugs were withdrawn at least 2 weeks before study entry. Patients received no additional antihypertensive therapy during the trial.

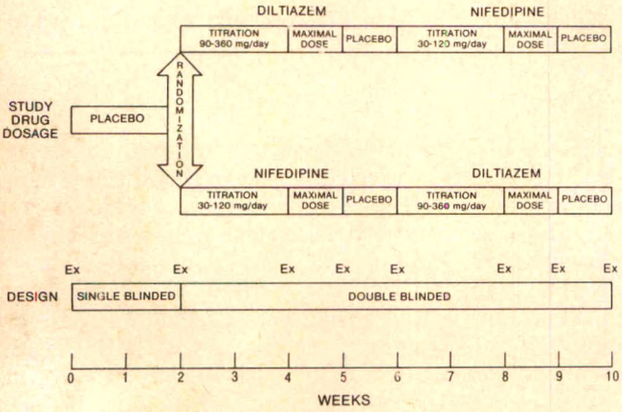

FIGURE 1. Study design: a 2-week, single-blind, placebo phase; double-blind randomization into diltiazem and nifedipine treatment groups; a 2-week dose-titration phase; followed by 1 week of maximal therapy. After a 1-week withdrawal schedule onto placebo, patients were crossed over to the other treatment schedule for a 2-week dose-titration phase and 1 week of maximal therapy. This was followed by a 1-week withdrawal schedule onto placebo. Standardized multistage graded exercise (Ex) tests were performed at the times indicated. Study drug doses are indicated for the dose-titration phase.

The blind protocol (Fig. 1) consisted of an initial 2-week, single-blind, placebo run-in period. During this time each patient received 2 placebo capsules 3 times a day, identical in appearance to the study medications. Patients who fulfilled all the inclusion criteria at the end of the second placebo run-in week entered the first drug treatment phase. During this phase, each patient received progressively increasing doses of either diltiazem (starting at 30 mg, 3 times a day, and increasing to 120 mg, 3 times a day) or nifedipine (starting at 10 mg, 3 times a day, and increasing to 40 mg, 3 times a day) as tolerated over the first 2 weeks of therapy. Patients were titrated to maximal dose or to appearance of adverse effects, and were then maintained on this dosage for an additional week. After the initial crossover period, the patients were abruptly discontinued from active therapy and were placed on placebo for 1 week. After completion of this second placebo period, each patient was crossed over to the other medication regimen, and the 3-week treatment period, as well as 1-week placebo withdrawal phase, was repeated.

Clinical observations: All patients kept a detailed daily record of anginal attacks and nitroglycerin tablets consumed. Supine and standing blood pressure and heart rate determinations were made once at the same time of the day, 2 to 5 hours after ingestion of placebo or the experimental drug. In this study, normalization of blood pressure was defined as a standing diastolic blood pressure of <90 mm Hg that was also reduced by at least 10 mm from the baseline value. Only the analyses of weeks 2, 5 and 9, when patients were on their highest doses of medication, are presented.

Exercise tolerance tests: Each patient underwent serial exercise tests at weeks 0, 2, 4, 5, 6, 8, 9 and 10 (Fig. 1). Multistage treadmill exercise testing consisted of sequential 3-minute stages of increasing workload, speed and elevation, using the Naughton protocol.[11] Tests were performed at approximately the same time of day and day of the week for each patient, when patients were in the postabsorptive state—approximately 2 to 5 hours after a dose. The stage at which each patient was started was individualized to attempt to have the patient reach exercise termination within 3 to 6 minutes. The stage for initiation was identical for each exercise test performed by a patient.

During exercise, blood pressure was measured every 3 minutes and lead V_5 was continuously monitored on an oscilloscope. The endpoints of exercise were either the onset of angina, an ST-segment change of ≥4 mm in the absence of anginal pain, a significant decrease in systolic blood pressure during exercise, the development of severe ventricular dysrhythmia (increased frequency of ventricular premature complexes), the occurrence of left bundle branch block or a high degree of atrioventricular block.

Measurements of heart rate, systolic and diastolic blood pressure and ST-segment displacement were obtained at the

last minute of each stage of exercise. The electrocardiogram was continually assessed for the occurrence of arrhythmias, and the rate-pressure product (systolic blood pressure × heart rate) was calculated. At the endpoint of exercise, each test was also analyzed for the maximal heart rate, systolic blood pressure and rate-pressure product achieved, total exercise duration (seconds), ST-segment displacement (mm) and reason for exercise limitation. The exercise work, expressed in kilopondmeters (kpm), was calculated from the formula: work (kpm) = $\sin\alpha \times$ speed (m/sec) × body weight (kg) × exercise time (seconds) × 10^{-3}, where α is the angle of inclination of the treadmill.

Plasma drug levels: Specimens for diltiazem and nifedipine plasma levels were obtained approximately 2 to 5 hours after drug ingestion, just before exercise testing. Drug levels for diltiazem were assessed with high-pressure liquid chromatography (Marion Laboratories, personal communication); those for nifedipine, with gas chromatography (Biodecision Laboratories, personal communication).

Statistical analysis: Group data are expressed as mean ± standard deviation in the text and tables, and as mean ± standard error of the mean in the figures. Differences were analyzed by the 2-tailed t test and were considered significant at the $p < 0.05$ level.

Results

All 10 patients who entered the study completed the trial and were titrated to dose levels of nifedipine, 10 to 40 mg, 3 times a day (mean 96 mg/day) and diltiazem 90 to 120 mg, 3 times a day (mean 342 mg/day). Mean blood levels of diltiazem at maximal doses were 279 ng/ml (range 96 to 507) and for nifedipine, 213 ng/ml (range 58 to 351). The plasma levels were within the therapeutic range for both drugs.

Effects on blood pressure and heart rate at rest: Results are shown in Table I and Figures 2 and 3. Compared with placebo, both diltiazem and nifedipine therapy produced significant reductions in supine and standing systolic and diastolic blood pressures. No significant differences between the antihypertensive effects of the 2 drugs were observed.

Normalization of blood pressure occurred with nifedipine in 8 of 10 patients; 8 of 10 responded to diltiazem in similar fashion (7 responded to both drugs). One patient, whose placebo baseline diastolic blood pressure was 100 mm Hg, had a diastolic blood pressure of 90 mm Hg on nifedipine (30 mg, 3 times a day) and 92 mm Hg on diltiazem (120 mg, 3 times a day). Another patient, who normalized on nifedipine, responded to diltiazem (120 mg, 3 times a day) with a diastolic blood pressure drop from 106 mm Hg baseline to 90 mm Hg. One more patient, who normalized on diltiazem, responded to nifedipine (40 mg, 3 times a day) with a diastolic blood pressure drop from 100 to 96 mm Hg on therapy. The patients who did not respond to active drug therapy had therapeutic plasma levels of the respective drugs. Overall, no correlation between plasma levels and blood pressure response was seen.

Diltiazem caused a reduction in standing heart rate ($p < 0.01$), but not supine heart rate. It also reduced the standing heart rate when compared with nifedipine ($p < 0.05$). Nifedipine caused a small, insignifi-

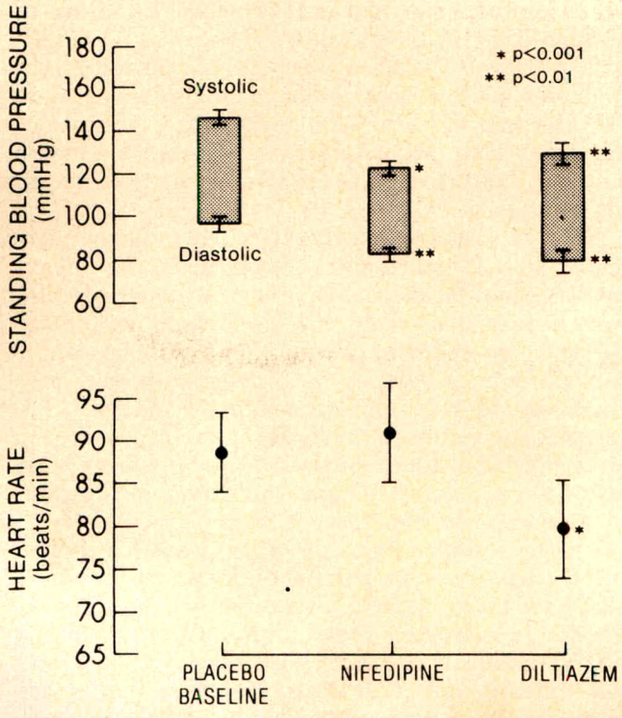

FIGURE 2. Standing blood pressure and heart rate at rest during placebo, nifedipine and diltiazem therapy. Comparisons are made with placebo baseline.

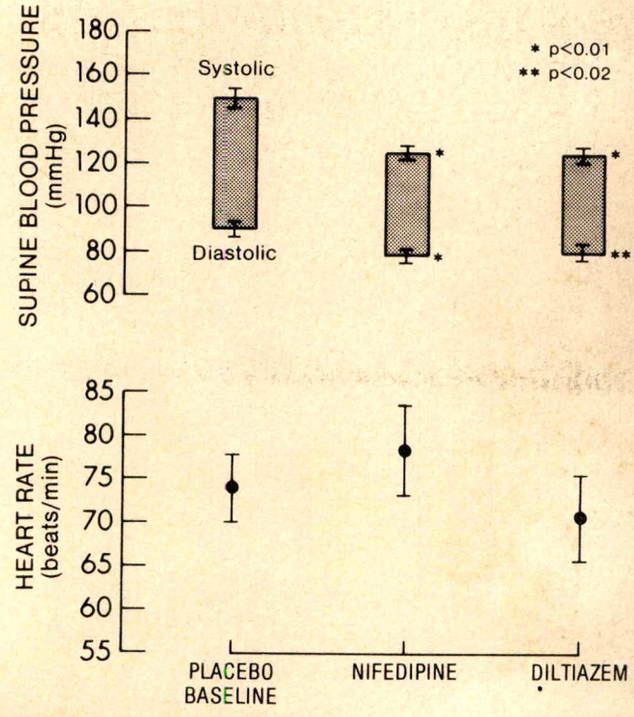

FIGURE 3. Supine blood pressure and heart rate at rest during placebo, nifedipine and diltiazem therapy. Comparisons are made with placebo baseline.

TABLE II Effects of Placebo, Nifedipine and Diltiazem on Anginal Symptoms, Exercise Tolerance and Exercise Variables

	Baseline (Placebo)	Nifedipine	Diltiazem	Statistical Significance: Placebo vs Nifedipine	Statistical Significance: Placebo vs Diltiazem	Statistical Significance: Nifedipine vs Diltiazem
Angina results						
Attacks/week	6.8 ± 3.4	2.9 ± 3.6	1.9 ± 2.1	p <0.001	p <0.01	NS
NTG consumption/week	4.7 ± 4.5	0.76 ± 0.89	1.1 ± 1.9	p <0.05	NS	NS
Stress test results						
Exercise duration (seconds)	268.2 ± 90.4	530.7 ± 159.2	562.8 ± 170.8	p <0.01	p <0.01	NS
Exercise work (kpm/10^3)	3.9 ± 3.7	10.1 ± 6.4	10.7 ± 4.8	p <0.01	p <0.01	NS
ST at end-exercise (mm) (maximum ST deviation)	1.0 ± 0.42	0.95 ± 0.62	1.3 ± 1.1	NS	NS	NS
Peak systolic BP (mm Hg)	178.2 ± 18.8	167.0 ± 22.0	170.2 ± 19.5	NS	NS	NS
Peak diastolic BP (mm Hg)	99.8 ± 10.2	86.0 ± 10.0	86.6 ± 10.5	p <0.02	p <0.01	NS
Peak heart rate (beats/min)	124.1 ± 19.9	128.0 ± 17.0	121.8 ± 16.5	NS	NS	p <0.05
Peak rate-pressure product (beats/min × mm Hg × 10^2)	221.2 ± 43.2	214.8 ± 46.4	209.1 ± 44.2	NS	NS	NS

NS = not significant; NTG = nitroglycerin; ST = segment depression.

TABLE III Effects of Placebo, Nifedipine and Diltiazem on the Rate-Pressure Product (beats/min × mm Hg × 10^2) Measured at Rest, Submaximal Exercise and Peak Exercise in Patients with Angina Pectoris and Hypertension

	Placebo	Nifedipine	Diltiazem	Statistical Significance: Placebo vs Nifedipine	Statistical Significance: Placebo vs Diltiazem	Statistical Significance: Nifedipine vs Diltiazem
Baseline	129.8 ± 22.1	111.3 ± 24.2	104.3 ± 30.4	p <0.01	p <0.01	NS
After 2 minutes of exercise	200.9 ± 45.5	160.7 ± 29.9	153.8 ± 27.3	p <0.01	p <0.001	NS
Peak	221.2 ± 43.2	214.8 ± 46.4	209.1 ± 44.2	NS	NS	NS

NS = not significant.

cant increase in standing and supine heart rate when compared with placebo.

Effects on angina pectoris: These results are shown in Table II and Figure 4. There was a reduction in the number of anginal attacks per week reported in patient diaries with both drugs. There was no significant difference between drugs in the magnitude of improvement in angina, although nifedipine was more effective than diltiazem in reducing nitroglycerin consumption from placebo baseline. Plasma drug levels were not indicative of the degree of improvement in anginal frequency.

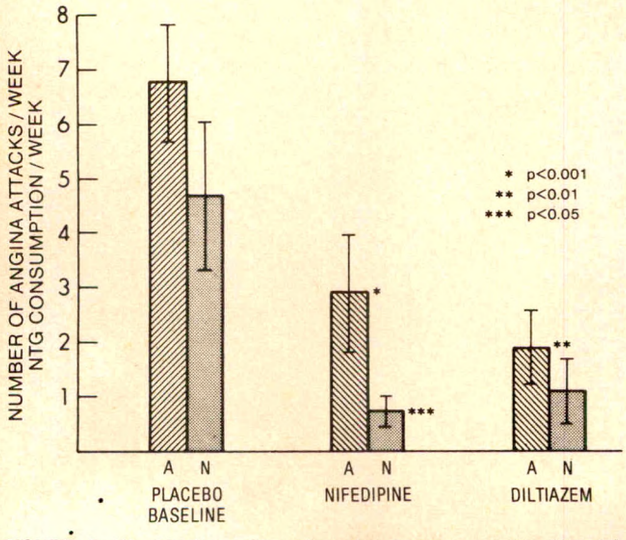

FIGURE 4. Weekly frequency of angina pectoris attacks (A) and nitroglycerin consumption (N) during placebo, nifedipine and diltiazem therapy. Comparisons are made with placebo baseline. NTG = nitroglycerin.

Effects on exercise variables: The results are given in Tables II and III and Figures 5 and 6. Significant increases in total exercise time and calculated exercise work were demonstrated with both nifedipine and diltiazem compared with placebo. There were no significant differences between the 2 drugs with respect to these variables. No differences in the maximal ST-segment deviation at exercise endpoint were seen among placebo, diltiazem and nifedipine. Plasma drug levels did not correlate with the degree of improvement in exercise tolerance.

The rate-pressure product at rest was lower than placebo baseline with both nifedipine and diltiazem ($p < 0.01$ for both). After 2 minutes of exercise, this reduction in mean rate-pressure product from placebo was maintained with both nifedipine ($p < 0.01$ and diltiazem ($p < 0.001$), with no significant difference observed between the active drugs. There was an observable blunting in the mean rate of rise of the rate-pressure product from rest to the 2-minute measurement in the nifedipine and diltiazem treatment

groups. At maximal exercise, there were no significant differences in mean rate-pressure products in the placebo, nifedipine and diltiazem groups. Neither nifedipine nor diltiazem significantly altered the peak mean systolic blood pressure or the peak mean heart rate when compared with placebo. However, the peak mean heart rate was higher ($p < 0.05$) in the nifedipine group compared with the diltiazem group. Peak mean diastolic blood pressure was maintained at a lower level with diltiazem ($p < 0.01$) and nifedipine ($p < 0.02$) than with placebo.

Adverse effects: Adverse effects reported by the patients on each of the drugs are seen in Table IV. Nine of 10 patients on nifedipine and 8 of 10 patients on diltiazem experienced at least 1 adverse effect. Overall, patients taking diltiazem had less complaints. One patient taking diltiazem (360 mg/day) developed Mobitz type I block and was withdrawn from dilitiazem therapy at the end of 2 weeks of active therapy.

TABLE IV Adverse Effects Reported by Patients While Taking Nifedipine and Diltiazem

	Nifedipine	Diltiazem
Palpitations	3	5
Shortness of breath	1	0
Heart block	0	1
Constipation	1	1
Facial flushing	1	0
Headache	3	2
Dizziness	3	2
Nervousness	4	1
Ankle edema	4	0
Other	8	3
Total	28	15

Discussion

Both diltiazem and nifedipine have potent antihypertensive actions.[3–5] The results of this double-blind, placebo-controlled study suggest that the drugs are also effective antihypertensive agents in patients with both angina pectoris and hypertension. Both drugs significantly reduced resting systolic and diastolic blood pressure in the standing and supine positions. All patients exhibited some reduction in blood pressure; in 8 of 10 patients on each drug the blood pressure was normalized.

One must be very careful when using arterial vasodilator drugs in hypertensive patients with angina pectoris, because these drugs often produce a sympathetically mediated reflex tachycardia, which may precipitate angina pectoris. Several studies have reported worsening of anginal symptoms in some patients on nifedipine therapy,[7,12–14] possibly related to reflex tachycardia. In our study, nifedipine produced no major change in heart rate, perhaps explaining how well the drug was tolerated. Diltiazem, which is a less potent vasodilator than nifedipine, also has direct depressant activity on sinoatrial automaticity,[10,15] and thus usually leaves the heart rate unchanged or decreased, as was observed in this study.

Effects on angina and exercise tolerance: Nifedipine and diltiazem are widely used in the treatment of patients with angina pectoris of effort.[6–10] In this study, both drugs were equally effective in reducing anginal frequency and in improving exercise tolerance in hypertensive patients with angina pectoris.

The maximal rate-pressure product observed during exercise on both diltiazem and nifedipine therapy was not significantly different from that during placebo. The drugs also did not reduce the level of ischemia at peak exercise, because similar degrees of ST-segment depression developed on active therapy and placebo. These observations suggest that the main pharmacotherapeutic action of these drugs in improving exercise tolerance is by reduction of myocardial oxygen consumption.[16] Therefore, the rate-pressure products at submaximal levels of exercise were reduced.

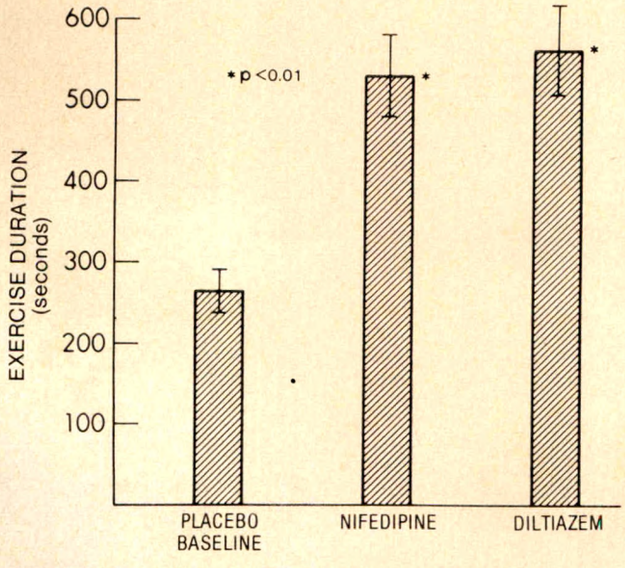

FIGURE 5. Treadmill exercise duration during placebo, nifedipine and diltiazem therapy. Comparisons are made with placebo baseline.

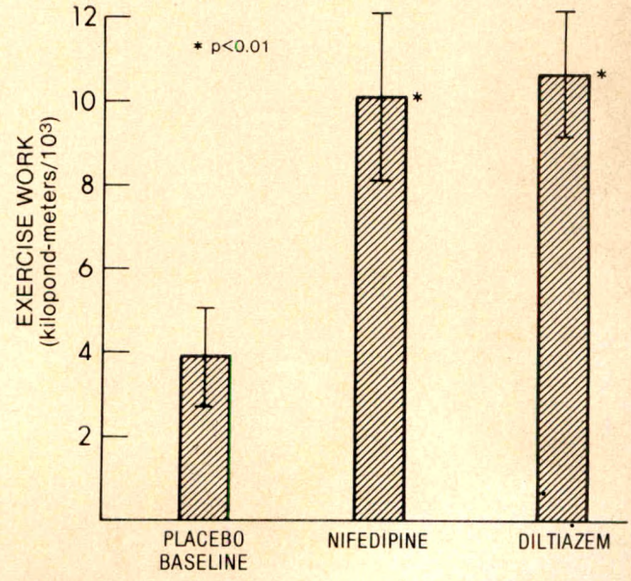

FIGURE 6. Treadmill exercise work during placebo, nifedipine and diltiazem therapy. Comparisons are made with placebo baseline.

Adverse effects: Diltiazem appears to be a better tolerated drug than nifedipine, with about half the number of reported adverse effects. One patient developed Mobitz type I heart block on diltiazem therapy, but this resolved with withdrawal of the drug. No other adverse effect necessitated cessation of therapy.

Clinical implications: In this study of hypertensive patients with angina pectoris, diltiazem and nifedipine were both shown to be safe and effective therapies for reducing attacks of angina pectoris, improving exercise tolerance and reducing elevated blood pressure. It is now evident that calcium channel entry–blockade can provide an alternative monotherapy to patients with both angina pectoris and systemic hypertension. Drug blood levels can be used to ensure compliance to treatment, but appear not to be helpful in predicting a clinical response. Because such patients are often on multiple medical regimens, simplification is often the key to improving patient compliance and, consequently, therapeutic outcome. Clinical experience is still needed for assessing possible interactions when calcium channel–blocking drugs are used with other agents commonly used in patients with both angina pectoris and systemic hypertension.

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Long-Term Renal and Systemic Effects of Calcium Entry Blockers in Normotensive and Experimental Hypertensive Dogs

BEN G. ZIMMERMAN, PhD, and JOAN L. GOERING, BA

The effect of diltiazem administered as a sustained infusion (10 to 15 μg/kg/min) was studied in 3 groups of conscious instrumented dogs: 4 normotensive, 5 Goldblatt hypertensive (GH) and 4 deoxycorticosterone acetate-salt treated Goldblatt hypertensive (DSGH) dogs. Mean arterial blood pressure, left renal blood flow and heart rate were monitored, and the plasma renin activity was determined in a control session and after 3 to 5 days of diltiazem infusion in the normotensive and after 5 to 8 days of infusion in the 2 hypertensive groups. Pressor and renal blood flow responses to phenylephrine, norepinephrine and angiotensin II were also determined in the control session and on the last day of the diltiazem infusion. Mean arterial blood pressure was found to be decreased at the 5 to 8-day interval in the DSGHs and in the GHs, but the change in the latter group was not statistically significant. Mean arterial blood pressure was unchanged in the normotensives. Renal vascular resistance was decreased by diltiazem in the normotensive group at 3 to 5 days and in the DSGHs at 1 to 2 days. Heart rate was not significantly affected by diltiazem in the hypertensive groups, but was increased in the normotensive group at the 1 to 2-day interval. Plasma renin activity tended to increase in the hypertensive, but not in the normotensive dogs. Pressor and renal blood flow responses to all the agonist agents tested were decreased in the presence of diltiazem. The hypotensive effect of diltiazem was more prominent in the conscious DSGHs than in the normotensive dogs or GHs; a decrease in renal vascular resistance was seen in both the normotensive and DSGH groups. Hypotension in these animals may be related at least in part to depression of vasoconstrictor stimuli.

(Am J Cardiol 1985;56:47H–51H)

Calcium entry blockers possess pharmacologic actions that make them potentially important agents for the treatment of essential hypertension. When administered on a long-term basis to hypertensive patients, nifedipine has a sustained hypotensive action; however, early in the treatment period, it evokes reflex increases in heart rate, plasma norepinephrine and renin levels.[1] Its blood pressure-lowering effect is attributable to relaxation of vascular smooth muscle—hence the vasodilatation—but a secondary action appears to intervene, which attenuates the baroreflex-induced tachycardia and renin release.[1,2] The mechanism of this secondary action has not been delineated. Because of the close relation between the kidney and hypertension, the actions of calcium entry blockers on renal function and hemodynamics are of particular interest. Recently, several renal effects of these agents have been uncovered; they appear to differ from those of classic vasodilator agents and may contribute to the overall usefulness of these blockers as antihypertensive agents. Systemic as well as intrarenal arterial administration of calcium entry blockers in short-term experiments have revealed a renal vasodilator action accompanied by increases in glomerular filtration rate and sodium excretion.[3–5] Interference with the intrarenal processes of tubuloglomerular feedback and renal blood flow autoregulation have also been demonstrated.[1,6] These effects are presumably due to the blockade of the action of calcium, upon which these processes may depend. Because most renal studies with the calcium entry blockers have been carried out for short time periods, little is known about the long-term renal effects of these agents.

The present investigation compared the renal hemodynamic and hypotensive effects of a sustained infusion of the calcium entry blocker diltiazem in normotensive and renovascular hypertensive dogs. We

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also wished to determine the effects of diltiazem on heart rate, plasma renin activity and response to pressor agents.

Methods

Experiments were conducted on 8 mongrel dogs of both sexes, weighing 19.7 to 25.4 kg each. The animals were quarantined until deemed healthy and immunized before use. Four normotensive and 6 Goldblatt hypertensive (GH) dogs were studied (Goldblatt hypertension was induced in 2 of the normotensive dogs). Chronic catheters (PE 50 tubing) were implanted in the femoral artery and vein for monitoring systemic arterial blood pressure and the intravenous injection of drugs, respectively. Arterial blood samples were withdrawn for plasma renin activity determination, using a previously reported radioimmunoassay technique.[7] Renal blood flow was measured from an implanted Zepeda blood flow probe (5 to 6 mm) in the left renal artery, connected to a Zepeda (SWF-4) electromagnetic flowmeter.[8] Mean arterial blood pressure and renal blood flow were monitored in the dogs while conscious and lying on a padded table. Experiments were conducted in the normotensive dogs after they had recovered from the surgical procedures. Two-kidney, 1-clip GH dogs were prepared by constriction of the right renal artery with an adjustable Goldblatt clamp. The clamp was tightened until renal blood flow was reduced by 75 to 80% of the control value as measured by electromagnetic flowmetry. An infusion pump (Infusaid Corp.) was implanted subcutaneously in the instrumented dogs in order to administer diltiazem chronically intravenously. A description of this technique was previously published.[9] The method of implantation (B. Wigness, unpublished observations) was as follows. A 10-cm incision was made parallel to the cranial edge of the infraspinous fossa, usually on the left side, beginning at the dorsal boundary of the scapula. A pocket for accommodating the pump was achieved by blunt dissection between the cutaneous trunci and the latissimus dorsi muscles. The pump was inserted and positioned between these muscles. Four ligatures were passed through loops on the pump using a surgical needle, and were tied carefully into the underlying muscle so as not to puncture the thorax. With the pump anchored into place, the catheter from the pump was led subcutaneously, the deep circumflex iliac or brachial vein was cannulated and the catheter was tied in place. Penicillin streptomycin (Vetycil) was injected into the pocket and the skin incision was sutured closed. The pump was filled with sterile water before implantation, and was refilled through the injection port when necessary. Water was infused for several days while the dog recovered from the implantation surgery. Infusion rates ranged from 6 to 13 ml/day, and the capacity of the pump was 50 ml. All operative procedures were carried out under aseptic conditions and penicillin streptomycin was administered on the day of surgery and when necessary thereafter.

Protocol: Experiments on the conscious dogs were begun by monitoring mean arterial blood pressure and renal blood flow until stable, and heart rate was then determined either by counting the arterial pulse or with a cardiotachometer (Beckman). These parameters were recorded on a Beckman R511 polygraph. A single 3-ml arterial sample was withdrawn for determination of plasma renin activity. Mean arterial blood pressure and renal blood flow responses to consecutive intravenous injections of phenylephrine hydrochloride (4 and 8 μg/kg), norepinephrine bitartrate (0.5 and 1 μg/kg) and angiotensin II (0.0125 and 0.05 μg/kg) were elicited to establish control pressor and renal vasoconstrictor effects. After this control experiment, the pump was emptied of its aqueous content with a syringe connected to a needle inserted into the injection port, which was palpated through the skin. Fifty milliliters of diltiazem solution at body temperature was used to prime the pump to provide a dose of 10 to 15 μg/kg/min throughout the period of drug treatment, which usually lasted 5 to 7 days. The pump was refilled periodically in order to provide a continuous infusion of the drug. The duration of infusion varied somewhat because of the few technical difficulties that developed in the course of the study. On the final day of drug infusion, the experiment with the agonist agents was repeated. This experimental protocol was used in the normotensive dogs, in the GH dogs (beginning $\bar{X} = 27$, range 11 to 67 days postclipping) and in the GH dogs given deoxycorticosterone acetate (DOCA)-salt (DSGHs) (5 mg DOCA and NaCl, 10 g/day).

Drugs used were l-norepinephrine bitartrate, l-phenylephrine hydrochloride, angiotensin II amide and diltiazem hydrochloride. Analysis of variance was performed on the data, using orthogonal contrasts to test for differences between means. Values are presented as the mean or mean ± standard error, and statistical significance was assumed at the level of $p < 0.05$.

Results

Effect of long-term infusion of diltiazem on blood pressure, renal vascular resistance, heart rate and plasma renin activity in normotensive and hypertensive dogs: Diltiazem infused at 10 to 15 μg/kg/min for 3 to 5 days in normotensive dogs pro-

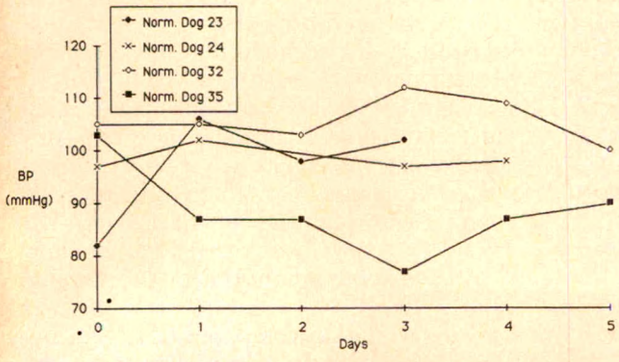

FIGURE 1. Mean arterial blood pressure (BP) in control period and during sustained infusion of diltiazem (10 to 15 μg/kg/min) in 4 normotensive (Norm) dogs.

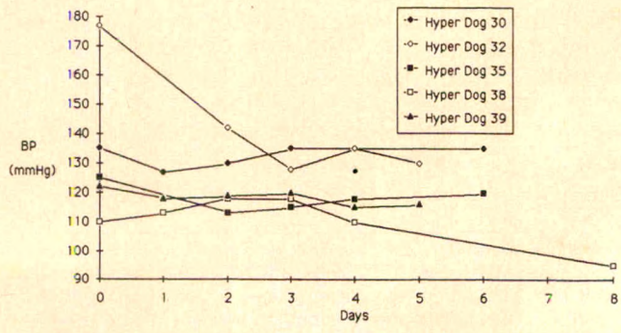

FIGURE 2. Mean arterial blood pressure (BP) in control period and during sustained infusion of diltiazem (10 to 15 μg/kg/min) in 5 Goldblatt hypertensive (Hyper) dogs.

TABLE I Effect of Sustained Infusion of Diltiazem (D) in Normotensive and Hypertensive Dogs

	MAP	RVR	HR	PRA
Normotensive				
Control	97 ± 4	0.66 ± 0.19	71 ± 2	1.28 ± 0.73
D, days 1–2	100 ± 4	0.62 ± 0.20	96 ± 14	
D, days 3–5	97 ± 2	0.54 ± 0.15*	75 ± 5	0.80 ± 0.13
Hypertensive				
Control	134 ± 10	0.92 ± 0.36	79 ± 10	2.03 ± 0.84
D, days 1–2	123 ± 5	0.73 ± 0.27	111 ± 7*	
D, days 5–8	119 ± 6	0.64 ± 0.22	90 ± 8	6.60 ± 2.5
DOCA hypertensive				
Control	133 ± 7	0.51 ± 0.04	91 ± 13	1.90 ± 1.12
D, days 1–2	115 ± 8	0.38 ± 0.07*	94 ± 10	
D, days 5–7	114 ± 5*	0.41 ± 0.07	87 ± 3	3.12 ± 0.96*

* $p < 0.05$ compared with control.
DOCA = deoxycorticosterone acetate; HR = heart rate (beats/min); MAP = mean arterial blood pressure (mm Hg); PRA = plasma renin activity (ng AI/ml/hour); RVR = renal vascular resistance (mm Hg/ml/min).

duced the changes in mean arterial blood pressure and the other parameters presented in Figure 1 and Table I. Variable changes in mean arterial blood pressure were seen in the normotensive dogs, with a decrease obtained in only 1 of 4. There was, however, a significant decrease in renal vascular resistance after 3 to 5 days of the diltiazem infusion. Heart rate increased in 3 of these 4 dogs during both time intervals, but the change was not significant. Plasma renin activity was not affected by diltiazem.

In GH dogs, diltiazem had a small effect on mean arterial blood pressure (Fig. 2 and Table I). At 1 to 2 days, only 1 of 5 dogs failed to respond, and at 5 to 8 days there was a modest decrease in mean arterial blood pressure in all. During diltiazem infusion, heart rate was significantly increased in the early interval, but returned to control levels at 5 to 8 days (Table I). Renal vascular resistance was not significantly affected by diltiazem in GH dogs. At 5 to 8 days, plasma renin activity was increased in 4 of the 5 dogs, but due to the variable change, the increase was not statistically significant.

Because diltiazem tends to increase plasma renin activity, and this is believed to antagonize the hypotensive effect of the drug,[2] we attempted to suppress the activity of the renin-angiotensin system in the GH dogs by administration of DOCA-salt. This approach was only partially successful because plasma renin activity was decreased to a negligible level in only 1 of 4 (Table I). Nevertheless, the DSGH dogs responded more consistently to diltiazem than the untreated GH dogs (Fig. 3 and Table I). Mean arterial blood pressure was reduced at 1 to 2 days in 3 of the 4, and was decreased in all 4 dogs at 5 to 8 days of the infusion. The rapid reversal of the hypotensive effect of diltiazem is seen in Figure 3. When the pump ran out of drug on day 4 of the infusion in dog no. 35, blood pressure promptly returned to the control level, and when the infusion was resumed, hypotension was reinstituted. Heart rate was variably affected by diltiazem in this group of animals, but plasma renin activity was increased significantly after 5 to 8 days of infusion.

Effect of long-term infusion of diltiazem on agonist-induced pressor and renal blood flow responses in normotensive and hypertensive dogs: Pressor (as Δ mm Hg) and renal blood flow responses (as percentage of decrease in renal blood flow) to phenylephrine, norepinephrine and angiotensin II in these groups of dogs are depicted in Figures 4 to 6. Responses were elicited in the control experiment and on the final day of diltiazem infusion (3 to 5 days in normal dogs and 5 to 8 days in hypertensive dogs). The magnitude of both the pressor and renal blood flow responses was similar in a given group of dogs; however, the renal blood flow response to angiotensin II tended to be greater in normotensive than hypertensive dogs. This probably reflected lower plasma renin activity in the normotensive group, because it is well known that the vascoconstrictor effect of angiotensin II is inversely related to plasma renin activity.[10,11] Generally, there was a uniform depression of both the pressor and renal blood flow response by diltiazem; however, the decrease in the pressor responses was not statistically significant in the normotensive group.

Discussion

Most previous investigations of the effect of calcium entry blockers on blood pressure and renal function

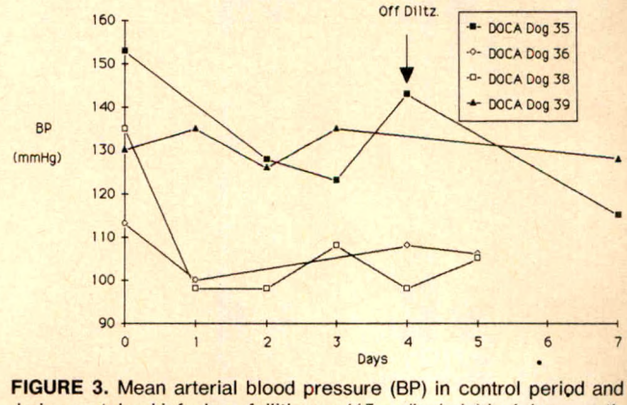

FIGURE 3. Mean arterial blood pressure (BP) in control period and during sustained infusion of diltiazem (15 μg/kg/min) in 4 deoxycorticosterone acetate (DOCA)-salt treated Goldblatt hypertensive dogs. Infusion ran out in dog no. 35 on day 4 (off Diltz.) and was resumed on day 5.

have dealt with their acute effects during intravenous or intrarenal arterial infusion.[3–5,12] It has generally been found that these agents decrease mean arterial blood pressure and increase heart rate, renal blood flow, glomerular filtration rate, sodium excretion and plasma renin activity. The vasodilator action of these agents has been considered responsible, either directly or indirectly, for these effects. Proportionately greater dilatation of the afferent than the efferent arterioles in the kidney would explain the increase in glomerular filtration rate. A selective antagonism by nisoldipine on the afferent arteriolar vasoconstriction caused by norepinephrine has also been reported.[13] Because certain calcium entry blockers, such as nifedipine and diltiazem, are used to treat hypertension, it is necessary to better understand their long-term influence on the cardiovascular system. Although the vasodilator action of these drugs accounts for the short-term cardiovascular and renal effects seen, there may be secondary actions that come into play to bring about sustained hypotension, and these are less well understood. We examined the long-term effects of diltiazem in the present study by using an intravenous infusion of a relatively high dose, 10 to 15 μg/kg/min, of the drug for about a week. Although some of our conclusions must be tempered because of the small number of animals studied, there appeared to be a difference in the response of the normotensive and hypertensive dogs to the sustained effect of diltiazem. Whereas the normotensive dogs did not exhibit a hypotensive effect, there was a modest though variable hypotensive response in both the GH and DSGH dogs. Some hypertensive dogs responded well while others exhibited only a slight decrease in mean arterial blood pressure.

Because the plasma renin activity was increased in both groups of hypertensive dogs (in 8 of 9 experiments in these 2 groups), it is likely that this was a factor contributing to their variable hypotensive response. Absence of an increase in the plasma renin activity in the normotensive group suggests that, in

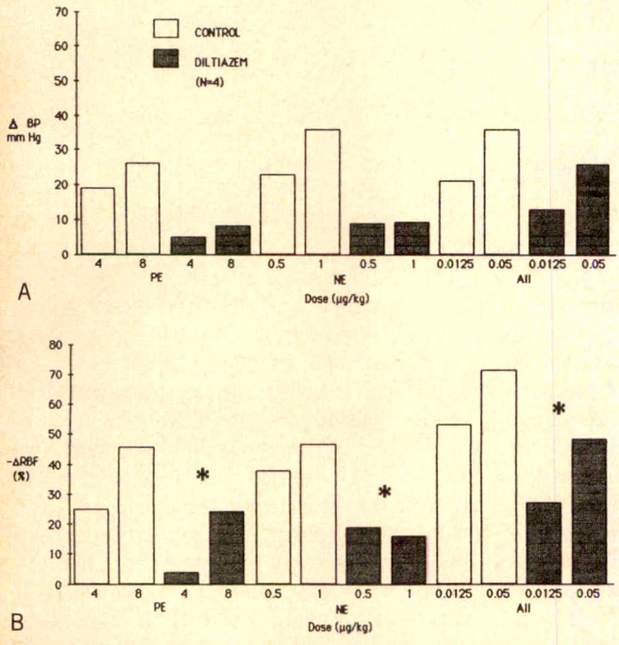

FIGURE 4. A, Blood pressure (Δ BP mm Hg) and **B,** renal blood flow (% Δ RBF) changes elicited by phenylephrine (PE), norepinephrine (NE) and angiotensin II (A II) administered intravenously in normotensive dogs before and during infusion of diltiazem (10 to 15 μg/kg/min).

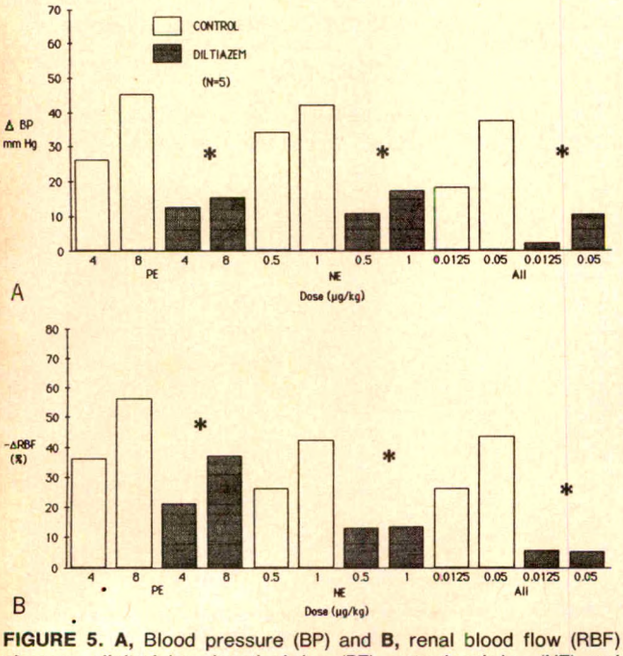

FIGURE 5. A, Blood pressure (BP) and **B,** renal blood flow (RBF) changes elicited by phenylephrine (PE), norepinephrine (NE) and angiotensin II (A II) administered intravenously in Goldblatt hypertensive dogs before and during infusion of diltiazem (15 μg/kg/min).

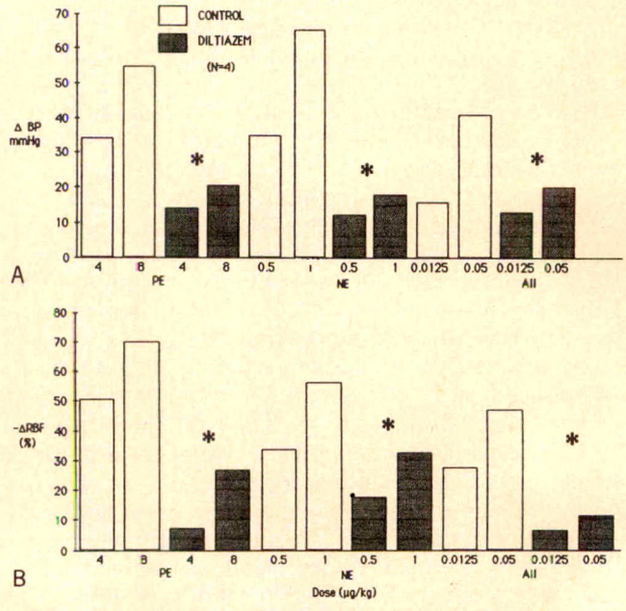

FIGURE 6. A, Blood pressure (BP) and **B,** renal blood flow (RBF) changes elicited by phenylephrine (PE), norepinephrine (NE) and angiotensin II (A II) administered intravenously in deoxycorticosterone acetate (DOCA) salt treated Goldblatt hypertensive dogs before and during infusion of diltiazem (10 to 15 μg/kg/min).

GH dogs, activation of the renin angiotensin system may be more sensitive to decreased calcium. It is known that renin release can be stimulated by removal of calcium from the medium perfusing of the kidney;[14,15] however, the relation between calcium and renin release in hypertension is not well defined. As with other investigators, we also found an increase in heart rate early after initiating administration of the calcium entry blocker in normotensive and GH dogs. This transient tachycardia was presumably due to the baroreflex evoked by the fall in mean arterial blood pressure. A variable renal vasodilator response to diltiazem was obtained in 2 of the 3 groups of dogs. In the DSGH dogs at 1 to 2 days and in normotensive dogs at 3 to 5 days, a significant decrease in renal vascular resistance was obtained during diltiazem administration. A generalized depression of reactivity to pressor agents was associated with the sustained decrease in mean arterial blood pressure caused by diltiazem. There have been numerous reports of marked attenuation of the pressor and vasconstrictor response to various agonists in vivo and to the contractile response of isolated vascular preparations in vitro by calcium entry blockers.[16–18] These observations were made during short-term administration of the drug, and it has not been substantiated that this is also a long-term effect. Some claim that the response to α_2 adrenoceptor agonists, and not α_1 adrenoceptor agonists, is depressed;[18] however, this point is controversial.

We also found a marked depressant effect of the renal vasoconstrictor response to pressor agents with short-term administration of diltiazem (unpublished observations). This depression of vascular reactivity appears to persist throughout the entire period of drug infusion as noted in the present study. In none of the 3 groups of animals was there evidence of a differential effect on the pressor agents studied. There was some variability within the animals, but the degree of depression of both the pressor and renal blood flow response to norepinephrine, phenylephrine and angiotensin II was about the same. Because these 2 adrenergic amines stimulate mainly α_1 adrenoceptors, and angiotensin II acts on its own receptors, inhibition of the vascular contractile response owing to stimulation at these sites was uniformly demonstrated. We did not see any clear indication of a relatively selective depression of the response to angiotensin II, as has been reported by others.[12] However, because our series was small, such an effect might have been uncovered by increasing the number of experiments. Also, the selectivity of action of calcium entry blockers may be a dose-dependent phenomenon. It would appear that the hypotension and decrease in renal vascular resistance that we observed in the present study are closely related to the depressed vascular reactivity obtained with diltiazem.

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The Kidney and Effective Antihypertensive Therapy

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Whether or not the kidney is involved in the genesis of hypertension in an individual patient, it becomes a major determinant of the response to antihypertensive therapy once a treatment strategy is adopted. The major mechanisms through which the kidney influences blood pressure are renin release and sodium retention, either together or separately, but additional mechanisms may also contribute. When sodium intake is restricted or a diuretic is used, the reactive increase in plasma renin activity makes a substantial contribution to limiting the blood pressure fall. When vasodilators or agents that block the sympathetic nervous system are used, sodium retention plays an important role. Among newer agents, the effectiveness of calcium channel blockers, converting enzyme inhibitors and perhaps dopamine analogs reflects, for reasons that differ from 1 class of agent to another, a special action on the kidney that limits the reactive renal response to the reduction in blood pressure. Treatment strategies that address the problem of the renal response are more likely to be effective than approaches that avoid or ignore it.

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Much of the strategy in designing antihypertensive therapy—a substantial amount of which was initially empirical—has involved the renal compensatory responses to the agents, whichever drug therapy was selected. Direct acting arteriolar vasodilators, for example, have always provided an attractive approach to the treatment of hypertension, because in most patients the hemodynamic defect responsible for the elevated pressure is an increase in peripheral resistance, at least partly mediated by vasoconstriction.[1] The use of nonspecific vasodilators has largely been limited by activation of compensatory systems,[2] including a prominent renal response that involves both retention of sodium and increase in renin release. This article will focus on some of the more practical implications of our increased understanding of the kidney's role in sustaining hypertension, however it is initiated.[3] A review of the functional abnormalities involving the renal blood supply in essential hypertension,[4–10] the role of newer pharmacologic agents in therapy[5,9–13] and the nature and extent of the reactive responses that often limit the effectiveness of therapeutic agents[2,5,12,14–16] is necessary to achieve this goal.

Investigators studying hypertension have several reasons for their long-standing interest in the renal blood supply as it affects glomerular filtration rate (GFR), sodium handling by the kidney and renal renin release. First, a reduction in renal blood flow due to renal artery stenosis is the most common curable form of secondary hypertension and is still believed by many investigators to contribute in some patients to the pathogenesis of essential hypertension. Second, whatever factors initiate the hypertension process in an individual patient, it is becoming evident that a renal response must be involved in order to sustain the elevated blood pressure.[3] Third, it is also becoming clear that the effectiveness of antihypertensive therapy, whatever agent is used, is determined to a substantial degree by the renal response. Finally, the continuing damage to the renal microvasculature by uncontrolled severe hypertension previously accounted for one of the major complications—uremia. The sharp reduction in the frequency of this complication is one of the triumphs of modern antihypertensive therapy.

A decrease in renal perfusion is common in essential hypertension; recent estimates suggest that about two-thirds of patients with essential hypertension have an inappropriately decreased renal blood flow.[7] Multiple lines of evidence now suggest that a functional disturbance—active vasoconstriction—plays a role in the abnormal renal perfusion and GFR in patients with essential hypertension. Renal perfusion varies in a moment-to-moment fashion much more in patients with essential hypertension than in normal subjects,

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an abnormality that must be due to active vasoconstriction.[7] Renal vasomotion is also increased in essential hypertension.[8] Moreover, when nonspecific vasodilators such as acetylcholine are administered into the renal artery, renal blood flow increases much more strikingly in patients with essential hypertension than in normal subjects.[4] With this potentiated renal vascular response, abnormalities in the renal arteriogram are reversed, often completely, by the vasodilators.

To the extent that such a functional abnormality involving the renal blood supply plays a role in the individual patient, one might anticipate that suitable doses of an appropriate vasodilator agent would reverse these abnormalities and thus improve renal perfusion and filtration rate. The renal response to therapy is conditioned to a major degree by both the relative influence of the fall in blood pressure and the direct and indirect effects of the therapeutic agent on the kidney.

Restriction of sodium intake is the simplest available therapeutic approach to hypertension. This maneuver reduces renal blood flow and GFR in animals and in man. The evidence is unequivocal that angiotensin-induced renal vasoconstriction, consequent to the reactive increase in renin release, accounts entirely for renal vasoconstriction.[6,17] There is now clear evidence that when diuretics are used as therapy, the reactive increase in plasma renin activity limits the fall in blood pressure.[11] Thus, it is reasonable to conclude that the decrease in renal blood flow and GFR induced by a diuretic is also angiotensin-mediated.

Because activation of the renin-angiotensin system plays such a central role in limiting the response to restriction of sodium intake and diuretics, it was reasonable to suspect that the addition of a β-adrenergic blocking agent—many of which block renin release when it is mediated by β-adrenergic receptors in the juxtaglomerular apparatus—would reverse the impact of restriction of sodium intake and diuretics on the kidney.[2] Unfortunately, propranolol, the most widely used and studied β-adrenergic blocking agent, directly induces renal vasoconstriction, apparently through an action on an α-adrenergic receptor in the kidney.[18] A propranolol-induced decrease in renal blood flow, with a parallel reduction in GFR, sodium retention and a reduced ability to handle sodium load, has also been well documented in man.[19] Although this renal response could be due to a decrease in cardiac output induced by the negative inotropic and chronotropic actions of these agents on the heart, it actually occurs with doses insufficient to influence cardiac output.[10] A similar renal response has been documented for a wide variety of β-adrenergic blocking agents including oxprenolol, pindolol, acebutolol, atenolol and dichloroisoproterenol.[9]

Renal vasoconstriction, however, is not an inevitable result of β-adrenergic blockade. Nadolol, a long-acting hydrophilic β-adrenergic blocking agent, induces a dose-related *increase* in renal blood flow over the dose range at which it decreases heart rate and thus cardiac output in man.[10] As opposed to the propranolol-induced decrease in sodium excretion, antinatriuresis did not occur with nadolol in the dog; indeed, nadolol increased sodium excretion (K. Duchin, unpublished observations). The clinical implication of this observation may be the remarkable frequency with which nadolol achieves goal blood pressure.[20] The Veterans Administration Cooperative Study Group reported that 77% of a large group of white subjects with mild to moderate essential hypertension achieved goal blood pressure with nadolol,[20] substantially more than achieved good blood pressure in a parallel study by the same Study Group on responses to other β blockers.[13]

What impact do the "nonspecific" vasodilators have on the kidney? This general class includes hydralazine, minoxidil, diazoxide, sodium nitroprusside and, in part, trimethapan.[15,16] The spectrum of their renal response is wide, but certain features are common to all. Despite the range of direct actions on the renal blood supply, sodium retention—often striking—occurs with *all*[15,16] and is the factor that limits their therapeutic efficacy.[14] The mechanism of the sodium retention has not yet been clearly delineated, but it is evident that the systemic response, especially the drop in blood pressure, plays an important role. For example, diazoxide is a potent renal vasodilator when infused into the renal artery, and this vasodilatation is accompanied by a striking *natriuresis*.[21] When the agent is given intravenously, however, an equally striking *antinatriuresis* occurs—presumably because of the blood pressure fall.[9,17,20]

The impact of these agents on renal blood supply and renal sodium handling when given systemically varies widely among individual patients, from a net increase to a net decrease in renal blood flow. However, antinatriuresis with sodium retention and, typically, a decrease in GFR occur, with even the most potent direct renal vasodilators in the series—hydralazine, diazoxide and minoxidil.[14–16,22,23] Thus, to date, selection of nonspecific vasodilators for the vasodilator action on the kidney has not spared the patient the negative renal influence of these agents.

Three new classes of agents have been developed that may have special implications for the kidney: calcium entry–blocking agents, converting enzyme inhibitors and dopamine analogs. Claims have been made that vasodilatation induced by calcium entry–blocking agents may be associated with less sodium retention.[24,25] However, rigorous evidence is not yet available, and the question remains controversial because the reports have involved small numbers of patients treated for a relatively short time. Calcium entry–blocking agents do provide an attractive potential. Diltiazem, 1 of the 3 calcium entry–blocking agents currently marketed in the United States, appears to have a special action on the renal blood supply, favoring a sustained or increased GFR and natriuresis despite the fall in arterial blood pressure.[26,27] The intriguing observation that normotensive offspring of hypertensive parents often show a potentiated renal vascular response to diltiazem[28] raises the interesting

possibility of a special renal action of this agent in essential hypertension.

The development of converting enzyme inhibitors provides a new approach to therapy and new tools for examining the underlying mechanisms of this disorder.[29] These agents are often effective even in severe hypertension, which has been resistant to standard triple therapy with a diuretic, hydralazine and a β-adrenergic blocking agent.[12] Recent studies suggest that this class of agents will exert an especially useful action on the kidney.[5,9] In patients with essential hypertension, the nonapeptide SQ 20881 induced a potentiated increase in renal blood flow[5] that was twice the increase in blood flow induced in normal subjects, despite a larger fall in blood pressure. Also, despite the fall in arterial blood pressure, SQ 20881 often induced an increase in GFR and, with it, natriuresis.[9] More recent studies performed with the orally effective analogs, captopril and enalapril, have shown a similar influence; the essential hypertensive patient enjoys a larger renal blood flow response and, despite the fall in arterial blood pressure, a well-maintained GFR.[31,32] Perhaps their influence on the kidney accounts for this class of agents' remarkable, often sustained impact on hypertension even in patients in whom traditional therapy has been ineffective.

The dopamine analogs, which are striking renal vasodilators in animal models,[32] have undergone too little study in man to allow any conclusion about their therapeutic potential.

What is the influence of antihypertensive agents on progression of renal microvascular abnormality to advanced nephrosclerosis and renal failure in hypertension? The impact of these agents is most evident when they are assessed in the treatment of severe hypertension already complicated by some degree of renal insufficiency. Three studies published in the past decade provide some insight and a relatively hopeful answer.[33–35] The 80 patients in the 3 studies were treated aggressively for prolonged periods. In each case, therapy for hypertension initially appeared to aggravate the already compromised renal function; however, with time and persistent lowering of the elevated arterial blood pressure, renal function usually improved, sometimes dramatically. In each study, a diuretic was used to reverse the sodium retention induced by dilators, and active vasodilators, especially hydralazine, methyldopa and oral diazoxide that were used for blood pressure control. In this population, in whom renal failure was the common mode of death—a 1-year mortality rate routinely exceeded 80% and was generally due to uremia—a striking improvement in natural history was obtained. One-year survival in the 3 series was 55, 76 and 80%—with stable or even improving renal excretory function.[33–35] Whether the newer vasodilators, calcium entry–blocking agents, converting enzyme inhibitors or dopamine analogs will produce an even more marked influence on natural history and renal function is not yet known.

In summary, the agents available to us for the treatment of hypertension have improved dramatically in the past decade and are likely to continue to improve over the next decade.[36] We have the luxury of being able to select our therapeutic objectives for the first time. Among the characteristics of new agents that are likely to be important, a salutary action on the kidney is high on the list.

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Calcium Entry Blockers: Antihypertensive and Natriuretic Effects in Experimental Animals

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Hypotensive and natriuretic effects of calcium entry blockers were studied in spontaneously hypertensive rats (SHRs) and normotensive Wistar Kyoto rats (WKYs). In SHRs, the hypotensive action of diltiazem was enhanced, while that of hydralazine was not different from its action in WKYs. Diltiazem, unlike hydralazine and nifedipine, did not cause reflex tachycardia in rats. Diltiazem and nifedipine caused an increase in urine volume and sodium excretion. The natriuretic potency of diltiazem was the same in both SHRs and WKYs and was not affected by pretreatment with indomethacin. Diltiazem increased plasma renin activity but had no influence on plasma aldosterone concentration. Hydralazine increased both plasma renin activity and plasma aldosterone concentration and decreased sodium excretion.

In anesthetized dogs, diltiazem increased sodium excretion, glomerular filtration rate and renal blood flow. Diltiazem may have a direct effect on tubular sodium reabsorption. This assumption was supported by a study with short-circuit current of the isolated bullfrog bladder. It is likely that diltiazem's effect of increasing urine volume and sodium excretion is due mainly to changes in renal hemodynamics and partly to direct action on renal tubules. Diltiazem opposed angiotensin II-induced responses, such as renal vasoconstriction and reduction of glomerular filtration rate. Under this condition, a marked natriuretic effect was observed with both intravenous and intraarterial administration of diltiazem. The ability to increase urinary excretion of sodium is a desirable characteristic for an antihypertensive agent. Calcium entry blockers have this ability and are therefore able to act without causing sodium and water retention.

(Am J Cardiol 1985;56:56H–61H)

Calcium entry blockers were developed mainly as antianginal agents and recently have been established as useful antihypertensive agents.

Reflex tachycardia and sodium retention are the main adverse effects of antihypertensive vasodilators such as hydralazine and minoxidil.[1–4] With this in mind, several studies have examined the effects of various calcium entry blockers on renal function.[5–7] When administered directly into the renal artery of anesthetized dogs, calcium entry blockers produced increases in urine volume and urinary excretion of sodium. However, the effect on the glomerular filtration rate (GFR) differed among calcium entry blockers.

Diltiazem, a typical calcium entry blocker, was given the code number CRD-401 in its early stage of development. C, R and D represented the coronary, renal and dextro isomer components of the compound, respectively. In other words, the vasodilating action of the renal artery along with that of the coronary artery was noticed in the very early stages of development.

This article reports the antihypertensive and natriuretic effects of diltiazem in spontaneously hypertensive rats (SHRs) and its renal effects in anesthetized dogs.

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Hypotensive Effects in Spontaneously Hypertensive Rats

Figure 1 shows the effects of diltiazem, hydralazine and nifedipine on blood pressure and heart rate in SHRs after oral administration. Blood pressure was measured by the tail-cuff method. As shown, all the drugs produced dose-dependent hypotensive actions. It is noteworthy, however, that hydralazine and nifedipine caused a marked increase in heart rate, whereas diltiazem showed a dose-related decrease.

In SHRs, a much higher dose of diltiazem than nifedipine was required to produce hypotension. However, in Grollman type 1-kidney renal hypertensive dogs, both drugs—orally and at the same doses (1 to 4

mg/kg)—caused hypotension to a similar extent.[8] The difference in the hypotensive doses of diltiazem between rats and dogs is considered to be due mainly to a difference in the metabolic pathway between the 2 animal species.[9,10] As shown in Figure 1, tachycardia induced by nifedipine was more marked than that caused by diltiazem. This indicates that reflex tachycardia is not a common feature of calcium entry blockers.

Figure 2 shows hypotensive actions of diltiazem and hydralazine in SHRs and normotensive Wistar Kyoto rats (WKYs) after oral administration. When changes in systolic blood pressure were expressed as percentages, hypotensive actions of hydralazine in SHRs did not significantly differ from those in WKYs. However, diltiazem showed a significantly stronger hypotensive action in SHRs than in WKYs.[11,12] The enhanced hypotensive action of diltiazem on hypertensive animals compared with normotensive control rats was also reported in deoxycorticosterone acetate-saline hypertensive rats[11,13] and in renal hypertensive rats.[12] Similar results were reported with nifedipine.[14] Therefore, hypotensive action seems to be a common characteristic of calcium entry blockers.

Natriuretic Effects in Spontaneously Hypertensive Rats and Wystar Kyoto Rats

Figure 3 shows the effects of diltiazem, hydralazine and nifedipine on urine volume and urinary excretion of sodium in SHRs. At doses causing a similar hypotensive action, diltiazem and nifedipine increased urine volume and sodium excretion in a dose-related manner. In contrast, hydralazine at a higher dose slightly increased urine volume but significantly decreased sodium excretion. This suggests that calcium entry blockers have different effects on renal function than those of such antihypertensive vasodilators as hydralazine.

We also examined the influences of orally administered diltiazem and hydralazine on plasma renin activity and plasma aldosterone concentration in SHRs. An arterial cannula was implanted in SHRs for blood sampling. Thirty minutes after drug administration, arterial blood was withdrawn from conscious subjects. Plasma renin activity and plasma aldosterone concentration were measured by radioimmunoassay. Hydral-

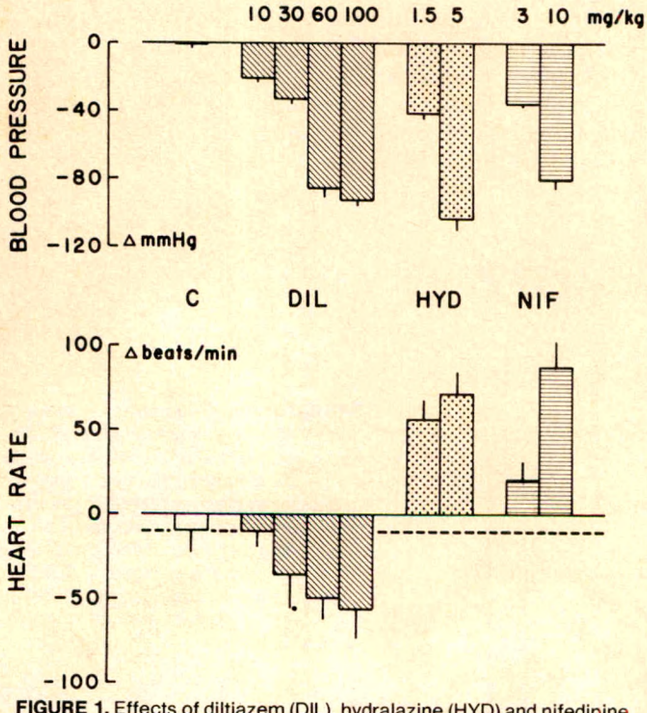

FIGURE 1. Effects of diltiazem (DIL), hydralazine (HYD) and nifedipine (NIF) on systolic blood pressure and heart rate in spontaneously hypertensive rats 1 hour after oral administration. Seventeen to 22-week-old male rats were used. Each column and vertical bar represent the mean ± standard error of 4 or 6 experiments. C = control.

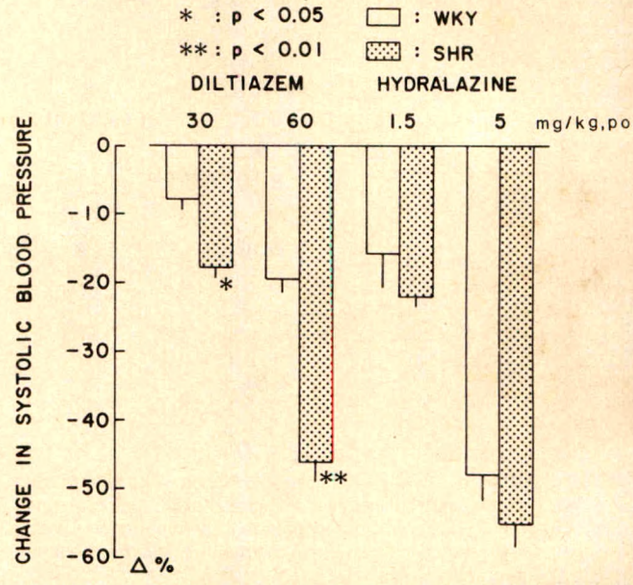

FIGURE 2. Hypotensive actions of diltiazem and hydralazine in spontaneously hypertensive rats (SHRs) and Wistar Kyoto rats (WKYs) 1 hour after oral administration. Each column and vertical bar represent the mean ± standard error of 4 to 6 experiments. Significance = compared with the corresponding values of WKYs.

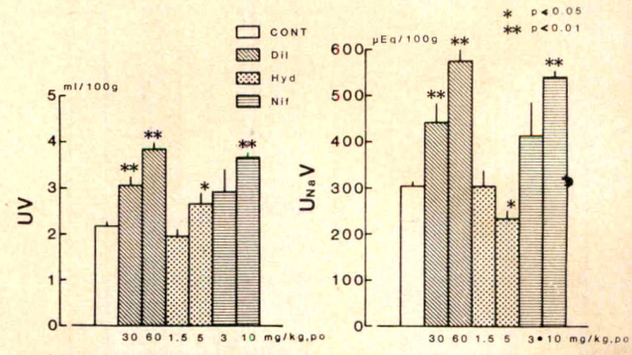

FIGURE 3. Effect of diltiazem (DIL), hydralazine (HYD) and nifedipine (NIF) on urine volume (UV) and urinary excretion of sodium ($U_{Na}V$) in saline-loaded spontaneously hypertensive rat. Physiologic saline (2.5 ml/100 g, body weight) was loaded twice at a 1-hour interval; urine was collected for 5 hours.

azine was shown to increase both plasma renin activity and aldosterone concentration; in contrast, diltiazem increased plasma renin activity without changing aldosterone concentration (Fig. 4).

No increase in plasma aldosterone concentration was reported with other calcium entry blockers.[15] In in vitro experiments, calcium entry blockers have been shown to inhibit angiotensin II-induced aldosterone release.[16–18] This may explain why calcium entry blockers produce no increase in plasma aldosterone concentration in conscious SHRs. In contrast, hydralazine increases plasma aldosterone concentration and may result in sodium retention.

In addition to the natriuretic effect of diltiazem after a single oral dose, we examined the effect of long-term treatment with diltiazem on body fluid distribution and plasma sodium concentration in SHRs.[12] Long-term administration of diltiazem (30 mg/kg day for 8 weeks) to young SHRs suppressed blood pressure

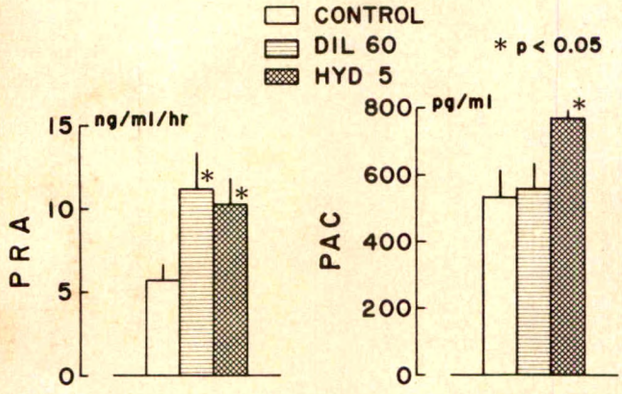

FIGURE 4. Influence of orally administered diltiazem (DIL) and hydralazine (HYD) on plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in conscious spontaneously hypertensive rats. Each column and vertical bar represent the mean ± standard error of the 5 to 6 experiments.

significantly during the development and at the plateau levels of hypertension, and caused no changes in body fluid distribution and plasma sodium concentration. These results are comparable with previous findings: diltiazem does not increase plasma aldosterone concentration, and it produces a natriuretic effect.

Mechanism of the Natriuretic Effect

The natriuretic effect of diltiazem was also examined in WKYs. Figure 5 shows that oral diltiazem, 60 mg/kg, produced marked increases in urine volume and urinary excretion of sodium. These effects of diltiazem in WKYs were as potent as its effects in SHRs. On the other hand, as shown in Figure 2, the diltiazem-induced hypotensive action was more potent in SHRs than in WKYs, and thus renal hemodynamics could be affected markedly in SHRs. Therefore, the natriuretic effect of diltiazem cannot be explained entirely by renal hemodynamic effects.

As shown in Figure 5, indomethacin did not affect the diltiazem-induced natriuretic effect in WKYs. Urinary prostaglandin E_2 excretion was significantly increased with the increase in urine volume as measured by radioimmunoassay. Even under conditions in which the excretion of prostaglandin E_2 was completely suppressed by pretreatment with oral indomethacin, 10 mg/kg, the increasing effects of diltiazem on urine volume and sodium excretion were not influenced. These results suggest that prostaglandin is not involved in the natriuretic effect of diltiazem.

In anesthetized dogs, renal function was studied by the clearance method under mild saline loading, and renal blood flow was measured by an electromagnetic flowmeter. When diltiazem was infused into the renal artery at a rate of 10 to 30 μg/kg/min, renal blood flow, GFR, urine volume and sodium excretion increased markedly.[5] Thus the natriuretic effect of diltiazem may be caused by changes in renal hemodynamics and an increase in GFR. When the renal blood flow was

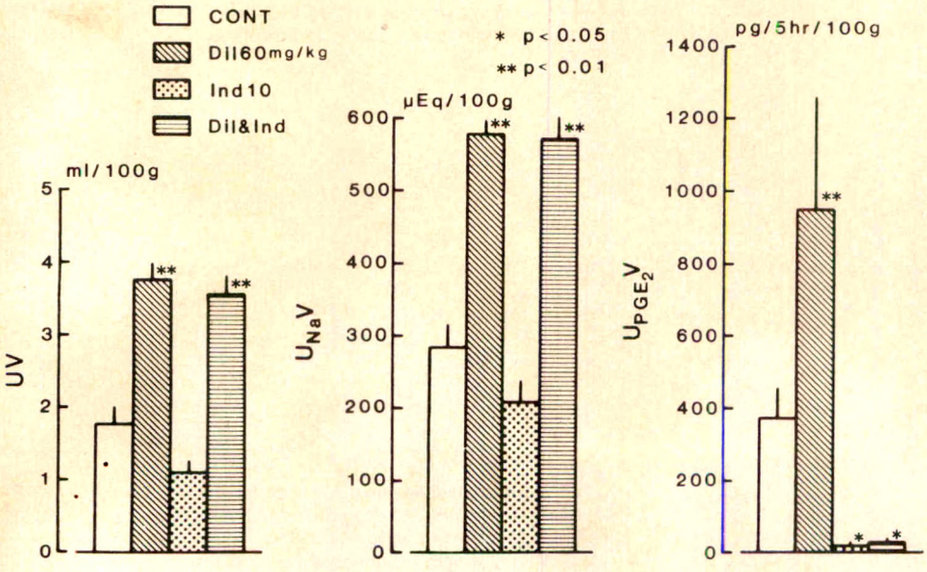

FIGURE 5. Natriuretic effect of diltiazem (DIL) in saline-loaded Wystar Kyoto rats in the presence and absence of indomethacin (IND.) Indomethacin was administered together with saline loading. Conditions of saline loading and urine collection were the same as those in Figure 3. Each column and vertical bar represent the mean ± standard error of 4 to 7 experiments.

kept constant with an aortic clamp during diltiazem infusion, sodium excretion was significantly increased but no change was observed in GFR and para-aminohippuric acid clearance.[5] The stopflow experiment under osmotic diuresis demonstrated that the sodium concentration of tubular fluid was elevated by diltiazem over the region corresponding to the distal segment of the nephron,[5] indicating that diltiazem suppressed the sodium reabsorption in the distal nephron. A similar result was also obtained by Abe et al.[19] Tsuchiya et al[20] studied the microautoradiographic distribution of carbon-14–labeled diltiazem in the dog kidney after renal arterial injection. They showed definite accumulation of radioactivity in the distal tubules that are involved in sodium transport. These results suggest that diltiazem-induced natriuresis is, at least in part, due to its direct action on renal tubules as well as to changes in the renal hemodynamics.

In the isolated bullfrog (*Rana catesbeiana*) urinary bladder, which is a model for the distal tubule, we assessed sodium transport by measuring short-circuit current using the method of Ussing and Zerahn[21] (Fig. 6). Diltiazem suppressed short-circuit current when applied to the serosal side. A weak but definite inhibition was observed when it was applied to the mucosal side. In this aspect, diltiazem contrasts with diuretics: hydrochlorothiazide and furosemide act selectively from the mucosal side, and ethacrynic acid acts selectively from the serosal side. These results support the hypothesis that the natriuretic effect of diltiazem is due to an inhibition of sodium reabsorption along the distal tubule as well.

Verapamil has been shown not to increase the GFR but is suggested to have a direct action on the renal tubule.[7,22] Inhibition by verapamil of short-circuit current has also been reported.[23] The natriuretic effect of nicardipine is explained by changes in renal hemodynamics and an increase in GFR.[6] Recently, the calcium entry blocker felodipine has been shown to inhibit sodium reabsorption at distal tubules using the micropuncture method in rats.[24]

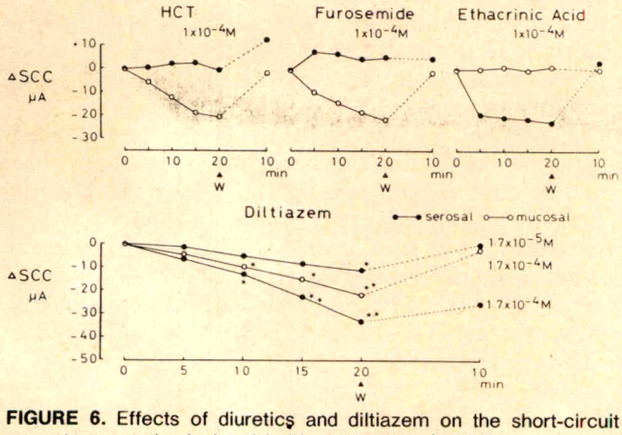

FIGURE 6. Effects of diuretics and diltiazem on the short-circuit current across the isolated bullfrog bladder. Δ SCC = change in short-circuit current; HCT = hydrochlorothiazide; W = wash. Each point represents: for diuretics, the mean of 3 experiments; for diltiazem, 1.7×10^{-5} *M*, the mean of 9 experiments; for diltiazem, 1.7×10^{-4} *M* (mucosal), the mean of 6 experiments; for diltiazem, 1.7×10^{-4} *M* (serosal), the mean of 8 experiments. Cord conductance was not changed for application of diltiazem or diuretics. * $p < 0.05$, ** $p < 0.01$ versus preadministration level.

Interaction with Angiotensin II

In anesthetized dogs, the vasodilating effect of diltiazem on renal vasculature when constricted by angiotensin II was more marked than when it was constricted by epinephrine.[5] Figure 7 shows the effect of intravenous administration of diltiazem on renal blood flow, urine volume and urinary excretion of electrolytes in anesthetized dogs with and without angiotensin II loading. Under the angiotensin II-unloaded condition, diltiazem tended to increase urine volume and sodium excretion when administered intravenously to dogs. However, diltiazem produced marked increases in urine volume and sodium excretion under the angiotensin II-loaded condition in which renal vas-

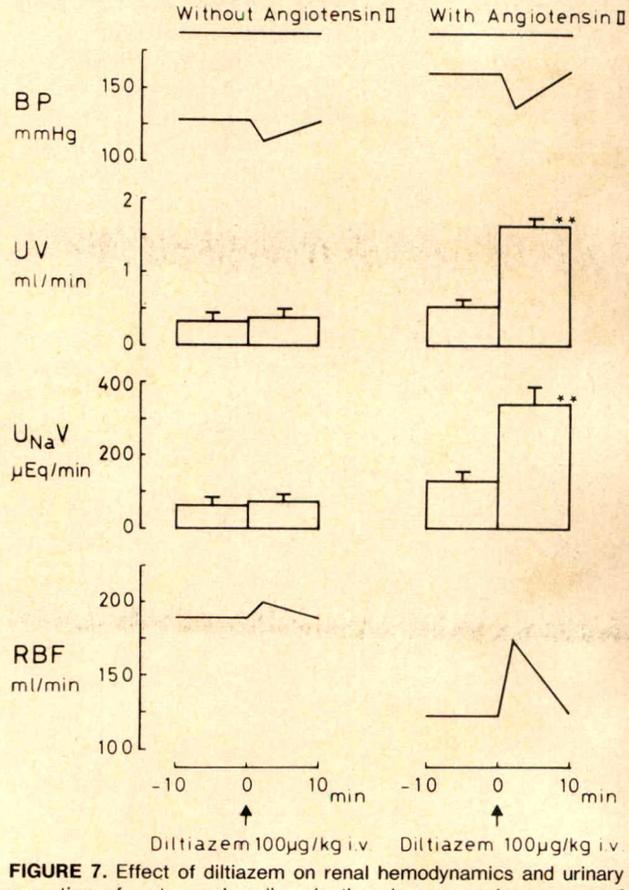

FIGURE 7. Effect of diltiazem on renal hemodynamics and urinary excretion of water and sodium in the absence and presence of angiotensin II loading in anesthetized dogs. Angiotensin II was infused intravenously at the dose of 0.25 μg/kg/min. Diltiazem was administered after urine flow became constant. BP = blood pressure; RBF = renal blood flow; UV = urinary volume; $U_{Na}V$ = urinary sodium excretion. Each column and vertical bar represent the mean ± standard error of 6 experiments. Blood pressure and renal blood flow are depicted as mean changes. Urine volume and urinary sodium excretion were determined by collecting urine for 10 minutes. ** $p < 0.01$ versus control.

cular resistance was doubled. The effect of diltiazem by intraarterial infusion on renal function was then studied using the clearance method. As shown in Figure 8, angiotensin II caused marked decreases in renal blood flow and GFR. Diltiazem caused increases in renal blood flow and GFR to levels higher than those before angiotensin II loading, and urine volume and sodium excretion were increased remarkably. In short, diltiazem noticeably improved renal function under conditions in which renal vascular resistance was elevated by angiotensin II.

Recently, glomerular mesangial cells have been studied as angiotensin II receptors regulating GFR.[25–27] Diltiazem inhibited contraction induced by angiotensin II in cultured mesangial cells.[28] As mentioned previously, diltiazem showed inhibitory effects on angiotensin II-induced responses in the renal vascular bed as well as reduction of GFR. It is possible that the increase in GFR by diltiazem results from the reduction of angiotensin II-induced contractions of renal vasculature and/or mesangial cells.

In summary, hypotensive and natriuretic effects of calcium entry blockers were studied in SHRs and WKYs. The hypotensive effects of diltiazem were more pronounced in SHRs than in WKYs, while hydralazine showed almost the same hypotensive activity in the 2 groups. This enhanced hypotensive action on hypertensive animals seems to be a common feature of calcium entry blockers. Diltiazem, unlike nifedipine or hydralazine, did not cause reflex tachycardia in either strain. In addition, diltiazem had no influence on plasma aldosterone concentration, although plasma renin activity was increased by the compound. On the other hand, both diltiazem and nifedipine at the same hypotensive doses increased urine volume and urinary excretion of sodium. The natriuretic effect of diltiazem was not affected by indomethacin, suggesting that prostaglandin is not involved in the natriuretic action of diltiazem. It was also found that long-term administration of diltiazem to young SHRs caused no change in body fluid distribution and plasma sodium concentration. In contrast to the effects of diltiazem, hydralazine decreased urinary sodium excretion and increased plasma aldosterone concentration. Plasma renin activity was also increased by hydralazine. It was shown that diltiazem is an antihypertensive agent with an enchanced hypotensive action in hypertensive subjects and does not cause tachycardia and sodium retention. Unlike hydralazine, diltiazem may not be associated with a decrease in antihypertensive activity during long-term treatment.

The effect of diltiazem on renal function was studied in anesthetized dogs. Diltiazem by intraarterial administration increased sodium excretion, GFR and renal blood flow. Therefore, changes in renal hemodynamics were likely to be responsible for the natriuretic effect of diltiazem. However, aortic clamp and stop-flow experiments suggested that diltiazem suppressed sodium reabsorption in the distal part of the nephron. The effect was supported by a study on short-circuit current applied to an isolated bladder preparation. It can be said that diltiazem's effect of increasing urine volume and urinary sodium excretion is due mainly to renal hemodynamics and partly to direct action on renal tubules. Diltiazem opposed angiotensin II-induced responses, such as renal vasoconstriction and reduction of GFR. In addition, under angiotensin II-loaded conditions, a remarkable natriuretic effect was observed after intravenous and intraarterial administration of diltiazem. This suggests that diltiazem improves renal hypofunction with an increase of mesangial cells. It also suggests that diltiazem is useful for the treatment of hypertension with increased renal vascular resistance.

Calcium entry blockers generally showed enhanced hypotensive effect in the hypertensive state, but induction of reflex tachycardia is not a common feature. The ability of calcium entry blockers to increase urinary excretion of sodium is a desirable characteristic for an antihypertensive agent. However, to what extent these natriuretic properties are involved in the antihypertensive effects should be examined for each calcium entry blocker.

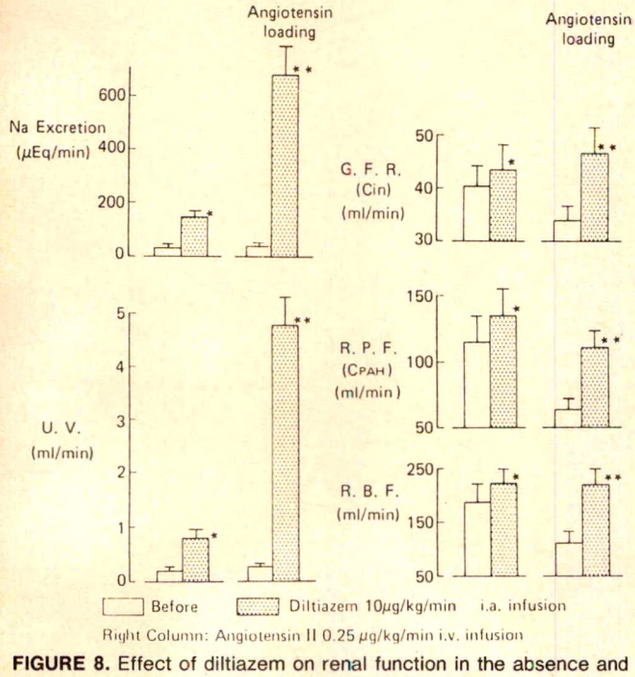

FIGURE 8. Effect of diltiazem on renal function in the absence and presence of angiotensin II loading in anesthetized dogs. Na = sodium; UV = urinary volume; GFR = glomerular filtration rate (insulin clearance); RPF = renal plasma flow (*p*-aminohippuric acid clearance); RBF = renal blood flow. Each column and vertical bar represent the mean ± standard error of 6 experiments. * $p < 0.05$, ** $p < 0.01$ versus before.

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Effects of Calcium Entry Blockers on Renin-Angiotensin-Aldosterone System, Renal Function and Hemodynamics, Salt and Water Excretion and Body Fluid Composition

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The renal effects of the calcium entry–blocking drugs diltiazem, nifedipine, verapamil and nitrendipine are reviewed. Although nifedipine stimulates plasma renin activity on a short-term basis, none of the calcium entry blockers produces a clinically significant sustained effect on any of the components of the renin-angiotensin-aldosterone system. Although all of the calcium entry blockers effectively lower blood pressure, none adversely affects renal function; glomerular filtration rate and effective renal plasma flow are maintained. Diltiazem may increase glomerular filtration rate via attenuation of the intrarenal effects of angiotensin II or norepinephrine. Although diltiazem and nifedipine increase salt and water excretion on a short-term basis, none of the calcium entry blockers produces a clinically significant sustained effect on salt and water excretion; serum electrolytes, urinary sodium and potassium excretion, body fluid composition and body weight are unchanged. Thus, calcium entry blockers can be expected to assume a prominent role in the treatment of hypertension because of their ability to lower blood pressure while preserving renal perfusion and function.

(Am J Cardiol 1985;56:62H–67H)

Although the calcium entry blockers were initially characterized by their pharmacologic ability to produce coronary vasodilation with myocardial depression, it has become clear that the individual members of this family of drugs differ not only in their pharmacokinetic properties, but also in their pharmacodynamic effects. Specifically, individual calcium entry blockers differ in regard to their effects on the myocardium (pacemaker activity, atrioventricular conduction, myocardial contractility), excitation-contraction coupling of smooth muscle (coronary, renal and peripheral vasculature) and stimulus-secretion coupling (juxtaglomerular cell renin secretion).

A large number of calcium entry–blocking drugs are currently undergoing clinical investigation, but only 4 drugs—diltiazem, nifedipine, verapamil and nitrendipine—have been studied sufficiently to permit some clinical individuation of their renal effects. Each of these 4 calcium entry–blocking drugs will be reviewed in terms of its known effects, both short- (response to an initial dose) and long-term, on the renin-angiotensin-aldosterone system, renal function and hemodynamics, salt and water excretion and body fluid composition.

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Renin-Angiotensin-Aldosterone System (Table I)

Diltiazem: Neither the intravenous administration of diltiazem nor its short-term oral administration (60 to 90 mg) produces a significant effect on recumbent plasma renin activity.[1–3] Long-term oral therapy (180 to 360 mg/day for 8 weeks) also has no consistent effect on recumbent plasma renin activity.[2–4] It is presumed that diltiazem has no effect on the circulating level of angiotensin II; however, the systemic vasoconstricting action of exogenously administered angiotensin II is significantly suppressed by the concurrent infusion of diltiazem.[1,3,5,6] The intravenous administration of diltiazem produces no significant effect on recumbent plasma aldosterone concentration.[1] We have observed that long-term oral diltiazem therapy (240 to 480 mg/day administered for 8 weeks to 17 hypertensive patients) has no significant effect on recumbent plasma aldosterone concentration: plasma aldosterone concentration was 6.2 ng/dl after both placebo and diltiazem therapy.

TABLE I Effects of Calcium Entry–Blocking Agents on the Renin-Angiotensin-Aldosterone System

	PRA	Angiotensin II	Aldosterone	Vascular Reactivity AII
Short-term				
Diltiazem	No Δ	No Δ	No Δ	Attenuation
Nifedipine	↑	↑	No Δ	Attenuation
Verapamil	No Δ	. . .	. . .	Attenuation
Nitrendipine	No Δ	. . .	. . .	. . .
Long-term				
Diltiazem	No Δ	. . .	No Δ	. . .
Nifedipine	No Δ	. . .	No Δ	No Δ
Verapamil	No Δ	. . .	No Δ	. . .
Nitrendipine	No Δ	. . .	No Δ	No Δ

Aldosterone = plasma aldosterone concentration; angiotensin II = plasma angiotensin II concentration; PRA = plasma renin activity; vascular reactivity AII = systemic vascular (blood pressure) response to exogenously administered angiotensin II during concurrent calcium entry–blocker therapy.

TABLE II Effects of Calcium Entry Blockers on Renal Function and Hemodynamics

	GFR	ERPF	RVR	Intrarenal Effects of AII
Short-term				
Diltiazem	No Δ ↑	No Δ ↑	. . .	Attenuation
Nifedipine	No Δ	No Δ	. . .	. . .
Verapamil	No Δ	. . .	. . .	Attenuation
Nitrendipine	. . .	. . .	. . .	. . .
Long-term				
Diltiazem	No Δ ↑	No Δ ↑	No Δ ↓	. . .
Nifedipine	No Δ	No Δ	. . .	. . .
Verapamil	No Δ	. . .	. . .	. . .
Nitrendipine	No Δ	. . .	. . .	. . .

ERPF = effective renal plasma flow; GFR = glomerular filtration rate; intrarenal effects of AII = GFR or ERPF response to exogenously administered angiotensin II during concurrent calcium entry–blocker therapy; RVR = renal vascular resistance.

Nifedipine: The short-term sublingual or oral adminstration of nifedipine (10 to 30 mg) to normotensive subjects or hypertensive patients produces a significant increase in plasma renin activity;[7–12] the effect peaks at 1 to 2 hours, returning to control levels at 4 hours.[7,10,11] This increase has been shown to be directly correlated with pretreatment plasma renin activity values[8,11] and inversely correlated with age.[9] However, long-term oral therapy (30 to 80 mg/day for up to 3 weeks) has no consistent effect on plasma renin activity.[8,12,13] The short-term oral administration of nifedipine significantly increases plasma angiotensin II concentration.[9] Nevertheless, neither short- nor long-term administration of nifedipine has an effect on plasma aldosterone concentration.[8,9,13] Although short-term intravenous administration of nifedipine to normotensive subjects has been reported to decrease significantly the pressor effect of exogenously administered angiotensin II,[14] long-term oral therapy (30 to 60 mg/day for 2 weeks) has no effect on the vasoconstrictor action of exogenously administered angiotensin II.[15,16]

Verapamil: Although the intravenous administration of verapamil to normotensive subjects increases plasma renin activity,[3] short-term oral administration (160 mg) produces no consistent effect.[10] Similar results have been reported in hypertensive patients after long-term administration of verapamil in dosages up to 480 mg/day for as long as 4 months.[13,17,18] However, the systemic vasoconstrictor action of exogenously administered angiotensin II is significantly suppressed by the concurrent infusion of verapamil.[3] Long-term oral administration of verapamil (240 mg/day) has no consistent effect on plasma aldosterone concentration.[13]

Nitrendipine: The short-term oral administration of nitrendipine (20 mg) to hypertensive patients has been reported to have no effect on plasma renin activity;[19] similar results have been reported after long-term therapy at dosges of up to 40 mg/day for 5 weeks.[20] Moreover, long-term nitrendipine administration does not attenuate pressor responses to exogenously infused angiotensin II.[20] Nitrendipine appears to have no effect on plasma aldosterone concentrations.[20]

Renal Function and Hemodynamics (Table II)

Diltiazem: The short-term oral administration of diltiazem (30 to 60 mg) to patients with existing arteriosclerotic cardiovascular disease (with or without hypertension) has been reported to have no consistent effect on either glomerular filtration rate (GFR) as measured by iodine-131 iothalamate or effective renal plasma flow as measured by I-131 hippuran, 3 hours postdosing.[21] A similar study in patients with chronic congestive heart failure showed no consistent effect on either GFR or effective renal plasma flow.[22] Studies in patients with primary or secondary renal disease have suggested that long-term oral diltiazem therapy (at dosages ranging from 30 to 120 mg/day from 1 week to 3 months) tended to increase GFR and effective renal plasma flow, the latter demonstrating the greater and more consistent change.[5,23–25] We studied 17 essential

TABLE III Effects of Diltiazem on Renal Function and Hemodynamics

	Placebo (4 weeks, n = 17)	Diltiazem (8 weeks, n = 17)
MAP (mm Hg) Mean ± SEM	122 ± 2	108 ± 3*
GFR (ml/min/1.73 m^2) Mean ± SEM	92 ± 8	92 ± 5
ERPF (ml/min/1.73 m^2) Mean ± SEM	343 ± 30	352 ± 23
Filt fract (%) Mean ± SEM	27.2 ± 1.1	27.4 ± 1.9
RBF (ml/min/1.73 m^2) Mean ± SEM	850 ± 74	861 ± 50
RVR (dynes s cm^{-5}/1.73 m^2 × 10^3) Mean ± SEM	13.5 ± 1.7	10.5 ± 0.6†

* $p < 0.0005$ compared with placebo.
† $p < 0.10$.
ERPF = effective renal plasma flow by para-aminohippurate; filt fract = filtration fraction = GFR/ERPF × 100; GFR = glomerular filtration rate by inulin clearance; MAP = mean arterial pressure = diastolic pressure + one-third pulse pressure; RBF = renal blood flow = ERPF/0.74/(1-Hct); RVR = renal vascular resistance = (MAP/RBF) × 80,000; SEM = standard error of the mean.

TABLE IV Effects of Diltiazem on Renal Function and Hemodynamics (initial GFR ≤80 ml/min/1.73 m^2)

	Placebo (4 weeks, n = 8)	Diltiazem (8 weeks, n = 8)
MAP (mm Hg) Mean ± SEM	119 ± 2	105 ± 3*
GFR (ml/min/1.73 m^2) Mean ± SEM	60 ± 6	89 ± 6*
ERPF (ml/min/1.73 m^2) Mean ± SEM	244 ± 30	339 ± 21†
Filt fract (%) Mean ± SEM	25.9 ± 1.9	26.8 ± 2.2
RBF (ml/min/1.73 m^2) Mean ± SEM	601 ± 76	837 ± 58†
RVR (dynes s cm^{-5}/1.73 m^2 × 10^3) Mean ± SEM	18.1 ± 2.8	10.3 ± 0.7††

* $p < 0.005$ compared with placebo.
† $p < 0.01$.
†† $p < 0.025$.
ERPF = effective renal plasma flow by para-aminohippurate; filt fract = filtration fraction = GFR/ERPF × 100; GFR = glomerular filtration rate by inulin clearance; MAP = mean arterial pressure = diastolic pressure + one-third pulse pressure; RBF = renal blood flow = ERPF/0.74/(1-Hct); RVR = renal vascular resistance = (MAP/RBF) × 80,000; SEM = standard error of the mean.

hypertensive patients receiving 240 to 480 mg/day of diltiazem for 8 weeks. Although mean arterial pressure decreased from 122 to 108 mm Hg, renal function and hemodynamics were not significantly altered (Table III). However, in 8 patients initially exhibiting a pretreatment GFR ≤80 ml/min/1.73 m^2, there was a marked increase (48%) in the rate (Table IV). Further, effective renal plasma flow and renal blood flow were increased, and renal vascular resistance was decreased. Short-term studies in animals, after either the intraarterial (renal) or intravenous infusion of diltiazem, have demonstrated diltiazem-induced dose-dependent increases in GFR and effective renal plasma flow.[26–29] Further, decreases in effective renal plasma flow induced by exogenously administered angiotensin II can be attenuated by concurrently administering diltiazem.[5,25,27]

Nifedipine: The short-term intravenous administration of nifedipine (1 mg) to patients with essential or renovascular hypertension has been reported to have no significant effect on either GFR as measured by inulin clearance or effective renal plasma flow as measured by p-aminohippurate clearance.[30] Similar results have been reported after the short-term oral administration of nifedipine (10 mg)[10,31] and after its more prolonged administration (40 mg/day for 1 to 3 weeks).[32,33] A recent report, however, has suggested that nifedipine may cause acute, reversible deterioration in renal function in patients with preexisting renal insufficiency.[34]

Verapamil: The short-term oral administration of verapamil (160 mg) has been reported to have no effect on creatinine clearance in either normotensive subjects or hypertensive patients.[10] Similar results have been reported after the long-term administration of verapamil in dosages ranging up to 480 mg/day for as long as 12 months.[17,18] Animal experiments, however, suggest that verapamil can reverse exogenous angiotensin II–mediated changes in the renal cortical microcirculation.[35] Specifically, verapamil inhibited angiotensin II–induced decreases in both the capillary plasma flow (mediated by efferent arteriolar vasocon-

TABLE V Effects of Calcium Entry Blockers on Salt and Water Excretion and Body Fluid Composition

	V	$U_{Na}V$	U_KV	PV/ECF	WT
Short-term					
Diltiazem	↑	↑	No Δ	. . .	. . .
Nifedipine	↑	↑	No Δ	. . .	. . .
Verapamil	No Δ	No Δ	No Δ	. . .	. . .
Nitrendipine	. . .	. . .	. . .	. . .	. . .
Long-term					
Diltiazem	No Δ	No Δ	No Δ	No Δ	No Δ
Nifedipine	No Δ	No Δ	No Δ	No Δ	No Δ
Verapamil	No Δ	No Δ	No Δ	No Δ	No Δ
Nitrendipine	No Δ	No Δ	No Δ	. . .	. . .

PV/ECF = plasma volume/extracellular fluid volume; U_KV = urinary potassium excretion; $U_{Na}V$ = urinary sodium excretion; V = urinary flow rate; WT = weight.

striction) and the ultrafiltration coefficient (mediated by mesangial contraction). These results suggest that calcium may be an important cofactor required for the expression of the intrarenal actions of angiotensin II.

Nitrendipine: Long-term oral nitrendipine therapy (10 to 40 mg/day for 5 weeks) has been reported to have no effect on the creatinine clearance of essential hypertensive patients.[20]

Salt and Water Excretion and Body Fluid Composition (Table V)

Diltiazem: The short-term oral administration of diltiazem (30 to 60 mg) to patients with either existing arteriosclerotic cardiovascular disease or chronic congestive heart failure has been reported to increase urinary sodium excretion, with the peak effect occurring 2 to 3 hours after dosing;[21,22] however, diltiazem had no effect on urinary potassium excretion. In patients with primary or secondary renal disease, the intravenous administration of diltiazem (10 to 40 mg over 10 minutes to 2 hours) has been reported to increase both urine flow rate and urinary sodium excretion.[25,36] However, the long-term oral administration of diltiazem, in dosages ranging up to 360 mg/day, has not been associated with changes in serum electrolytes or fluid retention as evidenced by edema or weight gain.[4,37] We have observed that long-term oral diltiazem therapy (240 to 480 mg/day for 8 weeks) administered to 17 hypertensive patients has no effect on serum electrolytes, body fluid composition or body weight (Table VI); further, long-term diltiazem therapy had no effect on salt and water excretion (Table VII).

A short-term study in dogs showed that the renal arterial infusion of diltiazem produces a prompt increase in urine flow, sodium excretion, osmolar clearance and free water clearance.[26] Yamaguchi et al[26] suggested that diltiazem has a direct effect on tubular sodium reabsorption because natriuresis could be maintained under conditions that prevented a drug-induced increase in effective renal plasma flow. A short-term study in rats demonstrated that diltiazem (30 to 60 mg/kg administered orally) significantly increased urine volume and urinary excretion of both sodium and potassium in a dose-related manner.[38] However, repeated oral administration (30 mg/kg/day for 8 weeks) had no effect on plasma sodium or potassium concentration, total body water, extracellular fluid or plasma volume, suggesting that diltiazem did not cause sodium or water retention.

TABLE VI Effects of Diltiazem on Body Fluid Composition and Weight

	Placebo (4 weeks, n = 17)	Diltiazem (8 weeks, n = 17)
RCM (liter) Mean ± SEM	2.0 ± 0.2	2.1 ± 0.2
PV (liter) Mean ± SEM	3.5 ± 0.3	3.4 ± 0.3
TBV (liter) Mean ± SEM	5.5 ± 0.5	5.5 ± 0.5
ECF (liter) Mean ± SEM	18.4 ± 1.4	18.9 ± 1.4
TBW (liter) Mean ± SEM	48.5 ± 3.4	46.5 ± 4.4
WT (kg) Mean ± SEM	89.5 ± 3.4	89.1 ± 3.4

ECF = extracellular fluid by $Na_2\ ^{35}SO_4$; PV = plasma volume by I-125 HSA; RCM = red cell mass by Cr-51 RBC; TBV = total blood volume = RCM + PV; TBW = total body water by ^3H_2O; WT = weight.

TABLE VII Effects of Diltiazem on Salt and Water Excretion

	Placebo (4 weeks, n = 17)	Diltiazem (8 weeks, n = 17)
$U_{Na}V$ (mEq/g creat) Mean ± SEM	115 ± 8	99 ± 12
U_KV (mEq/g creat) Mean ± SEM	38 ± 5	40 ± 6
FE_{Na} (%) Mean ± SEM	1.7 ± 0.3	1.1 ± 0.2
FE_K (%) Mean ± SEM	11.5 ± 1.9	11.3 ± 1.9
V (ml/min) Mean ± SEM	10.3 ± 1.5	10.8 ± 1.2
C_{H_2O} (ml/min/1.73 m^2) Mean ± SEM	7.4 ± 1.2	6.7 ± 1.1

C_{H_2O} = free water clearance; FE_K = fractional potassium excretion × 100; FE_{Na} = fractional sodium excretion × 100; U_KV = 24-hour urinary potassium excretion; $U_{Na}V$ = 24-hour urinary sodium excretion; V = urinary flow rate.

Nifedipine: The acute intravenous administration of nifedipine (1 mg) to patients with essential and renovascular hypertension was reported to increase urine flow rate and sodium clearance.[30] Similar results have been reported after short-term oral administration of nifedipine (10 mg);[10] there was no effect on potassium excretion. Long-term studies, however, do not support sustained diuretic or natriuretic effects. Long-term nifedipine therapy (in dosages ranging up to 60 mg/day) does not significantly alter serum or urinary electrolytes,[16,32,39] plasma volume[12,13] or body weight.[13,16,32,33,40]

Verapamil: Neither short-term oral administration of verapamil (160 mg)[10] nor long-term oral therapy (dosages ranging up to 480 mg/day for as long as 2 weeks)[18] has an effect on urinary flow rate or sodium or potassium excretion in either normotensive subjects or hypertensive patients. Further, long-term verapamil therapy is not associated with significant changes in serum electrolytes,[35] plasma volume[13] or body weight.[13,40,41]

Nitrendipine: Long-term oral nitrendipine therapy (10 to 40 mg/day for 5 weeks) has no significant effect on urinary excretion of sodium or potassium.[20]

Conclusions

Renin-angiotensin-aldosterone system: Because calcium may inhibit renin secretion by a direct action on the juxtaglomerular cell,[42] the administration of a calcium entry–blocking drug might be expected to stimulate renin secretion. However, only nifedipine, the most potent peripheral vasodilator of the drugs studied, consistently produces this effect; and it does this only after short-term administration. None of the other calcium entry–blocking drugs produces a clinically significant alteration, after long-term administration, in any of the components of the renin-angiotensin-aldosterone system. Although the acute systemic vasoconstricting action of exogenously administered angiotensin II is attenuated by a concurrent infusion of diltiazem, nifedipine or verapamil —presumably by decreasing the sensitivity of the vasculature to angiotensin II by preventing an increase in cytosol-ionized calcium—this effect is lost after the long-term administration of either nifedipine or nitrendipine. Thus, calcium entry blockers appear to have little or no influence on the renin-angiotensin-aldosterone system as it relates to systemic blood pressure control.

Renin function and hemodynamics: Among the calcium entry–blocking drugs currently under study, only diltiazem has been shown to increase GFR or effective renal plasma flow and to decrease renal vascular resistance. None of these calcium entry–blocking drugs adversely affects renal function or hemodynamics. There are at least 2 potential mechanisms for the observed increase in GFR or effective renal plasma flow after diltiazem therapy: reversal of angiotensin II–induced vasoconstriction (mesangium or efferent arteriolar tone) and reversal of norepinephrine-induced vasoconstriction (mesangium or efferent arteriolar tone). The nonspecific effect of calcium entry blockers to prevent an increase in cytosol-ionized calcium would be expected to decrease the sensitivity of the renal vasculature and the mesangium to both angiotensin II and norepinephrine. Indeed, several investigators have demonstrated that diltiazem and verapamil attenuate the intrarenal effects of both exogenously administered angiotensin II[5,26,27,35] and norepinephrine.[43] In addition, diltiazem and verapamil have been shown to differentially affect α-adrenergic receptors. Both drugs preferentially antagonized postsynaptic (voltage-activated calcium channel) α_2-adrenergic receptors.[44–46] Diltiazem and verapamil selectively interfere with the vasoconstrictor action of norepinephrine on the afferent arteriole (suggesting a greater density of α_2 receptors), while leaving intact its action on the efferent arteriole (suggesting a greater density of α_1-adrenergic receptors).[43] Our observation that GFR increased in hypertensive patients, when initially impaired, without an associated increase in the filtration fraction, supports the differential effect of norepinephrine on the renal vasculature, but does not exclude the possibility of a reversal of a direct angiotensin II or norepinephrine effect on the glomerulus (mesangium). Reversal of angiotensin II-mediated–efferent arteriolar vasoconstriction would have been expected to disproportionately enhance effective renal plasma flow, decreasing the filtration fraction.

Salt and water excretion and body fluid composition: Activation of renal α_2 adrenoceptors increases renal retention of sodium and water (this is mediated by inhibition of adenylate cyclase; reducing cyclic adenosine monophosphate diminishes the flux of sodium and water through the wall of the proximal tubule in the lumen).[47,48] Thus, antagonism of renal α_2-adrenergic receptors by a calcium entry–blocking drug might be expected to enhance sodium and water excretion. However, only diltiazem and nifedipine have been shown to induce natriuresis and diuresis on a short-term basis. More important, none of these calcium entry–blocking drugs was shown to have a clinically important sustained effect on salt and water excretion. This conclusion is supported by the absence of an observed effect of calcium entry blockers on serum electrolytes, body fluid composition or body weight. However, anecdotal case reports do attest to the potential for these drugs to produce edema. The frequency or mechanism for this potential adverse effect is unclear. Because the calcium entry–blocking agents generally lower blood pressure without producing salt and water retention, these drugs can be expected to assume a prominent role as first-step therapy in the treatment of patients with hypertensive diseases.

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Renin, Calcium Metabolism and the Pathophysiologic Basis of Antihypertensive Therapy

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The renin-angiotensin-aldosterone system regulates blood pressure and volume homeostasis in addition to sodium and potassium metabolism, and may be linked to divalent cation metabolism as well as hypertensive disease. In essential hypertension, circulating serum magnesium and Ca^{++}, and the calcium regulating hormones, parathyroid hormone, calcitonin and 1,25 dihydroxyvitamin (1,25D) are different in the various renin subgroups. Elevated blood pressure induced by such maneuvers as dietary salt loading is associated with exacerbations of these calcium metabolic deviations, and appears related to salt-induced changes in serum Ca^{++} or 1,25D levels. Short- or longer-term lowering of blood pressure with the calcium-channel blocker, nifedipine, or with calcium or magnesium supplementation is associated with a shift of renin system activity and calcium metabolic indexes back to average normotensive values in those subjects most susceptible to these hypotensive agents.

These observations suggest that deviations in calcium metabolism in essential hypertension may be related to the pathophysiology of the hypertensive process. Further, renin system activity and calcium metabolic indexes such as serum Ca^{++} levels may help target specific subgroups of hypertensive populations most susceptible to various dietary or drug maneuvers, and thus may provide a basis to better understand and treat clinical hypertension.

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Increased blood pressure is an abnormal physical sign that we appreciate as varying quantitatively in degree; however, we have often mistakenly considered it qualitatively as a single homogeneous entity. It is not. Our present knowledge of hypertension, the spectrum of biochemical and hormonal parameters contributing to hypertension and the varying clinical responses to therapeutic maneuvers all testify to the heterogeneity of hypertension. Thus, it would appear most reasonable to attempt therapeutic intervention on the basis of our ability to analyze the pathophysiology of hypertension for an individual patient. Assessment of the renin-angiotensin-aldosterone system by simple blood and urine measurements makes this effort realistic and practical, and we have used it for over a decade.

We will review how the renin system operates physiologically as a vasoconstriction-volume control system, consider evidence for the clinical and biochemical heterogeneity of hypertension based on analysis of renin-sodium profiling and, finally, suggest how knowledge of renin system activity provides a rational basis for therapeutic choices in hypertension. This approach not only highlights the relevance of renin activity to hypertension, but also, interestingly, establishes a basis for understanding the contribution of calcium metabolism to the pathogenesis and therapy of hypertensive disease.

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The renin-angiotensin-aldosterone system and vasoconstriction-volume analysis of blood pressure regulation: Renin was initially identified over 85 years ago as a pressor substance obtained from saline extracts of rabbit kidney,[1] but its relevance was not commonly appreciated until the classic experiments of Goldblatt et al,[2] who established renin as a humoral substance capable of causing hypertensive disease. Thereafter, renin was identified as an enzyme initiating a biochemical cascade that also involved angiotensin converting enzyme, and resulted in the formation of angiotensin II as an active effector molecule.[3,4] The connection of this biochemical cascade to potassium and sodium-volume homeostasis was advanced by Laragh and others who established that adrenal aldosterone production was chiefly regulated by angiotensin II,[5] as well as by potassium.[6] While further advances in our knowledge of the renin-aldosterone system continue, the system as it functions in the peripheral circulation has been defined (Fig. 1).[7]

Renal renin secretion is stimulated by a variety of hemodynamic, hormonal and ionic signals associated with decreased "effective" circulating blood volume, decreased blood pressure or other stress responses.[7] Increased circulating active renin (plasma renin activity) catalyzes the hydrolysis of plasma renin substrate, a protein of liver origin. This results in increased formation of angiotensin I, the C-terminal 10 amino acid fragment of plasma renin substrate. Angiotensin converting enzyme acts on angiotensin I by hydrolyzing the distal 2 amino acids to produce the 8 amino acid peptide, angiotensin II. Although the angiotensin converting enzyme is present in all vascular endothelial cells, most circulating angiotensin II is produced within the pulmonary vascular bed.[8] Angiotensin II acts directly as a vasoconstrictor to increase blood pressure, an effect magnified by its ability to release catecholamines in the periphery. A longer-term effect of angiotensin II is its ability to stimulate adrenal aldosterone production, which, in the presence of sufficient dietary sodium, causes renal sodium retention, increased pressor sensitivity to angiotensin II, volume expansion and/or increased blood pressure. Thus, the original signals for renin release are dampened by increased pressure or volume retention, suppressing renin secretion and operating as a classic negative feedback system (Fig. 1). Concurrent effects on potassium metabolism are regulated at the renal level, preventing abnormalities of volume or pressure from resulting in abnormal potassium metabolism.[9]

On the basis of these considerations, blood pressure may be considered to be dependent on 2 types of factors. Vasoconstrictor factors affect pressure by changing the tone of the blood vessel wall, altering internal vessel diameter and thus pressure. Volume factors alter the amount of circulating fluid present for any given amount of vasoconstrictor tone, and thus also directly affect pressure. Normally these 2 types of factors are balanced in see-saw fashion to maintain normal blood pressure and tissue perfusion under a variety of dietary and environmental circumstances. Indeed, there is a characteristic inverse, hyperbolic relation between circulating plasma renin activity and urinary sodium excretion, reflecting dietary sodium intake (Fig. 2). This relation, by defining the normal

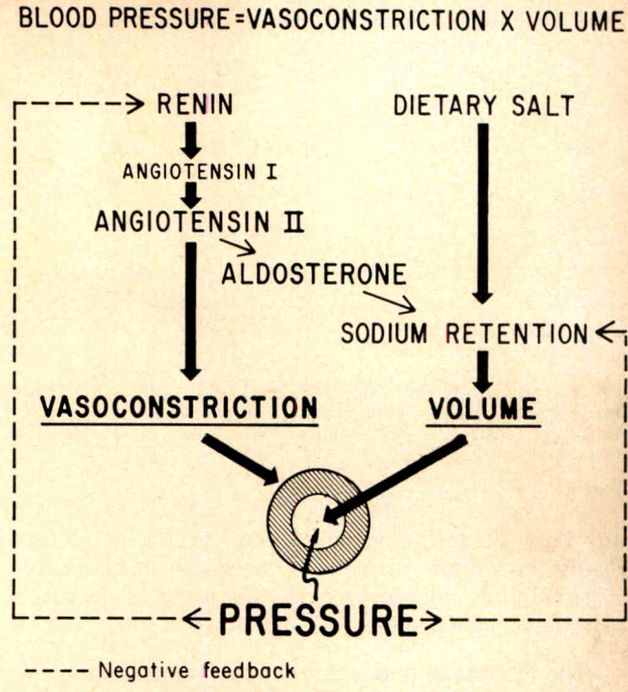

FIGURE 1. The renin-angiotensin-aldosterone system as a coordinate blood pressure and sodium-volume control system. Reproduced with permission from WB Saunders.[7]

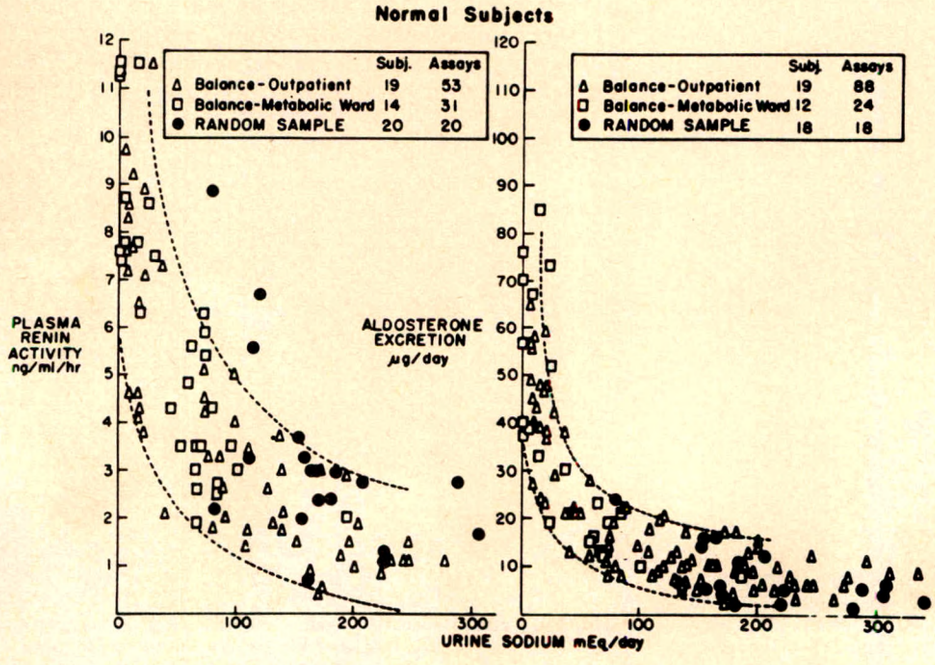

FIGURE 2. Relation of plasma renin activity and urinary sodium excretion to 24-hour urinary sodium in normotensive subjects. Reproduced with permission from WB Saunders.[7]

TABLE I Calcium-Regulating Hormones in Essential Hypertension

Group	PTH (pg/ml)	CT (pg/ml)	1,25D (pg/ml)
NI-BP (n = 10)	244 ± 21	68.0 ± 6.5	53.9 ± 5.3
Lo-RH (n = 18)	433 ± 38†	56.4 ± 1.8*	77.4 ± 5.4*
NI-RH (n = 19)	318 ± 22*	66.2 ± 4.0	57.2 ± 4.3
Hi-RH (n = 11)	292 ± 37	84.3 ± 3.9*‡	44.1 ± 4.9‡

* $p < 0.05$ versus NI-BP.
† $p < 0.005$ versus NI-BP.
‡ $p < 0.001$ versus Lo-RH.
PTH = parathyroid hormone; CT = calcitonin; 1,25D = 1,25 dihydroxyvitamin D; NI-BP = normotensive control subjects; Lo-RH = low renin hypertensives; NI-RH = normal renin hypertensives; Hi-RH = high renin hypertensives.

link between sodium-volume and constrictor factors regulating volume-pressure homeostasis in man, provides valuable clues and a clinically practical approach to hypertensive disease.

The Hormonal and Biochemical Heterogeneity of Hypertension

Renin profiling in hypertension: If the same type of analysis, comparing plasma renin activity with ambient 24-hour sodium excretion, is attempted for subjects with essential hypertension, certain hypertensive subjects demonstrate an inappropriate excess of renin activity at levels of urinary sodium excretion normally associated with inhibition of renin secretion. On the other hand, another, larger group of hypertensive subjects—approximately 30%—have suppressed levels of plasma renin activity, even when, at a low urinary sodium excretion, one would expect a stimulation of renin secretion (Fig. 3). These deviations of plasma renin activity at a given level of urine sodium excretion from the tight correlation observed in normotensive subjects serve as the basis for "renin profiling," and define "high renin" and "low renin" essential hypertension as opposite clinical subgroups. In high renin hypertension, the excess pressure is usually renin dependent, while in low renin states, the renin system acts as if an excess of volume factors are present, not dependent on renin activity.[7]

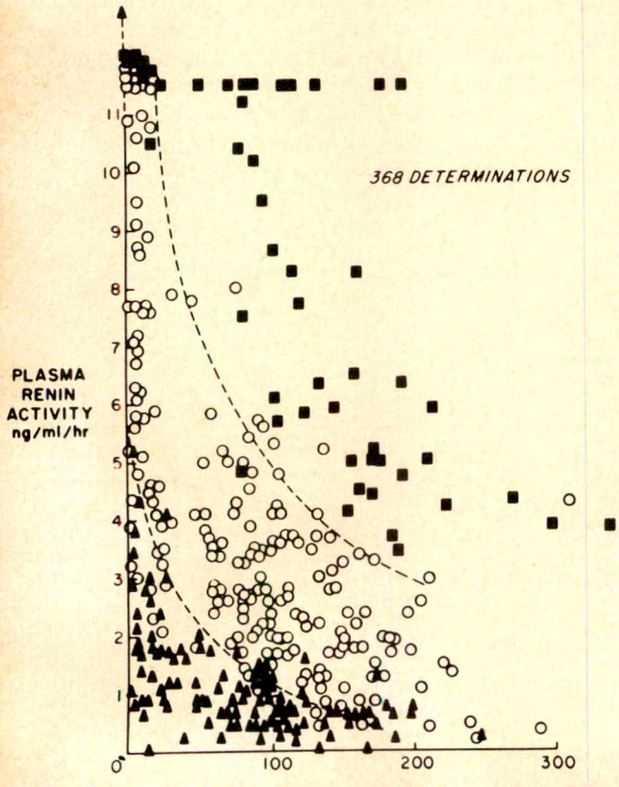

FIGURE 3. Relation of plasma renin activity to 24-hour urinary sodium excretion in hypertensive subjects. Dashed lines represent limits of plasma renin activity values for normotensive subjects at a given level of urinary sodium. (▲, ○ and ■ define low, normal and high renin hypertensives, respectively.)

Abnormalities of calcium metabolism in hypertension: While calcium has long been linked to the molecular events of muscle contraction, abnormalities of calcium metabolism in hypertensive disease have only recently been appreciated.[10] Further, no coherent picture has emerged of the specific manner in which these variously described abnormalities contribute to elevations in blood pressure.

We recently defined renin-linked heterogeneous deviations of calcium metabolism among subjects with essential hypertension, suggesting a state of calcium surfeit in some individuals, and of calcium deficit in others. Thus, the seemingly paradoxical and contradictory observations previously described may each be relevant in differing renin subgroups of hypertension. Specifically, serum Ca^{++} is directly related to plasma renin activity; low renin subjects have lower average Ca^{++} than either high renin hypertensive or normotensive control subjects. Serum magnesium is inversely related to plasma renin activity; low renin subjects have higher levels than other hypertensive or normotensive subjects (Fig. 4).[11]

The significance of these serum ionic alterations is further emphasized when calcium-regulating hormones are similarly analyzed. Serum levels of calcitonin, 1,25 dihydroxyvitamin D (1,25D) and parathyroid

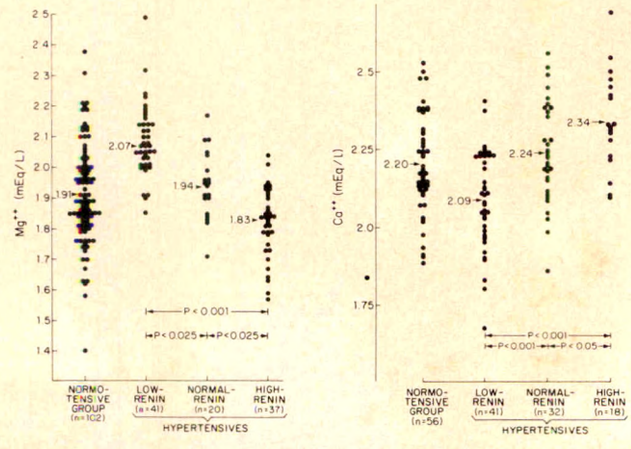

FIGURE 4. Serum levels of magnesium, **left,** and ionized calcium, **right,** in normotensive and low, medium and high renin subgroups of hypertensive subjects. Reproduced with permission from N Engl J Med.[11]

TABLE II Metabolic and Hormonal Comparison of Salt-Sensitive Versus Salt-Insensitive Subjects with Longer-Term Salt Loading

Group	ΔDBP (%)	PRA (ng/ml/hour)	ΔCa_{io} (mEq/liter)	ΔCT (%)	Δ1,25D (%)
Salt-sensitive (n = 8)	9.4 ± 0.9	1.5 ± 0.5	−0.08 ± 0.04	−26 ± 6	68.5 ± 9.0
Salt-insensitive (n = 5)	0.25 ± 1.3	3.0 ± 0.6*	+0.14 ± 0.05†	+1.6 ± 6	18.0 ± 17.7

* $p < 0.02$.
† $p < 0.01$ versus salt-sensitive.
DBP = diastolic blood pressure; PRA = plasma renin activity; Ca_{io} = serum ionized calcium; CT = calcitonin; 1,25D = 1,25 dihydroxyvitamin D.

hormone also vary among renin subgroups of essential hypertension (Table I). Calcitonin levels were lower in low renin subjects and higher in high renin subjects, as compared with either other hypertensive or normotensive control subjects, while levels of 1,25D were highest in low renin subjects compared with high renin hypertensive or normotensive control subjects. Parathyroid hormone levels were also highest in low renin hypertensive subjects.[12] These hormonal deviations were appropriate for the changes in serum Ca^{++} and highlight the biologic rather than just the statistical significance of the initially observed serum ionic deviations. Further, they suggest a broad-based link between the control of calcium metabolism and renin system activity in essential hypertension, and emphasize the pathophysiologic basis of renin profiling. Indeed, as we have suggested, plasma renin activity may reflect as well as modulate the steady-state distribution of calcium and magnesium across cell membranes.[11]

Clinical Heterogeneity of Hypertension—Salt Sensitivity, Calcium and Magnesium Supplementation

The question that naturally arises at this stage is what, if anything, might these linked ionic and hormonal deviations have to do with hypertension? Our preliminary observations suggest that blood pressure responses to varied dietary sodium intakes, as well as the ability of calcium and magnesium supplementation to affect blood pressure, differ among different renin subgroups of essential hypertension and can be predicted by either renin-sodium profiling or assessment of calcium metabolism.

Sodium sensitivity: Essential hypertensive outpatients, randomly allocated for 3 to 4 weeks each to low (<50 mEq/day) and high (>200 mEq/day) dietary sodium intakes, had blood pressure measurements, renin-sodium profiling and calcium metabolic variables analyzed. When categorized as sodium sensitive versus insensitive (Δ diastolic pressures >5% on high versus low sodium), sodium-sensitive subjects had significantly lower plasma renin activity, significant suppression of serum Ca^{++} and a greater elevation of 1,25D compared with sodium-insensitive subjects (Table II). Indeed, regardless of the definition of sodium sensitivity, continuous relations were observed between the change in pressure on high versus low dietary sodium and the changes in either serum Ca^{++} ($r = -0.90$, $p < 0.001$) or 1,25D ($r = 0.74$, $p < 0.01$).[13,14] Identical results were obtained when subjects were studied as inpatients on metabolic balance diets of low (10 mEq/day) and high (200 mEq/day) sodium content for 5 to 7 days each (Figs. 5 and 6).[15] Thus, it seems that blood pressure elevations with increased

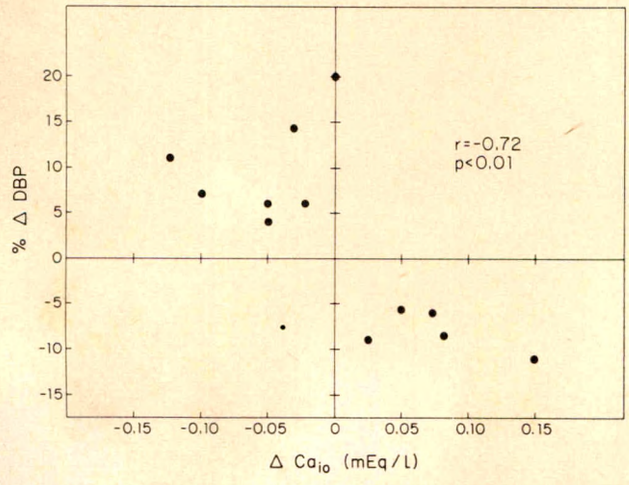

FIGURE 5. Effect of high versus low dietary salt intake on diastolic blood pressure as it relates to salt-induced changes in serum ionized calcium concentrations. %ΔDBP = percent change in diastolic blood pressure; ΔCa_{io} = change in serum ionized calcium.[15]

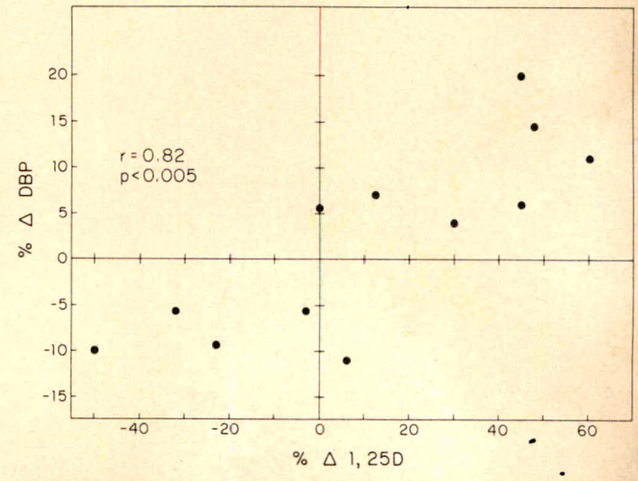

FIGURE 6. Effect of high versus low dietary salt intake on diastolic blood pressure as it relates to salt-induced changes in serum 1,25 dihydroxyvitamin D levels. %ΔDBP = percent change in diastolic blood pressure; %Δ1,25D = percent change in 1,25 dihydroxyvitamin D (data from references 14 and 15).

dietary sodium intake are characteristic of the low renin subject, that a unique calcium ionic and hormonal profile defines the sodium-sensitive state and that alterations in calcium metabolism may mediate the phenomenon. Regardless of pathophysiology, however, renin-sodium profiling and analysis of calcium metabolic indexes seem useful in identifying the sodium-sensitive subject. This has also been suggested by investigations of a putative natriuretic hormone in volume-related hypertension.[16]

The hypotensive efficacy of calcium and magnesium supplementation: Not only can renin activity and calcium indexes predict the spectrum of blood pressure responses to different dietary sodium intakes, but a similar analysis describes the effects of calcium and magnesium loading as well. We[17] and McCarron and Morris[18] reported preliminary results in treating essential hypertension subjects with oral calcium supplementation. In each study, blood pressure declined in some, rose in others and did not significantly change in many.[17,18] When these results were further analyzed by comparing the blood pressure response of an individual person with the pretreatment plasma renin activity or serum Ca^{++}, significant relations were observed. Calcium administered orally as the carbonate salt, 2 g/day for 5 days, to subjects on metabolic balance diets, preferentially lowered pressure in subjects with lower initial levels of renin activity ($r = 0.89$, $p < 0.005$) or lower initial levels of serum Ca^{++} ($r = 0.82$, $p < 0.005$).[19] Higher serum Ca^{++} levels or plasma renin activity were associated with either no clinical response or even a pressor response. Thus, we may be able to target specific hypertensive subgroups for whom calcium supplementation would be of benefit.

The exact opposite pattern of blood pressure response was observed with magnesium loading. Subjects on metabolic balance diets were given 2 g/day $MgSO_4$ intramuscularly for 3 to 5 days. Blood pressure was selectively lowered in normal and high renin subjects, while low renin subjects actually experienced a net pressor response (Fig. 7). Altogether, there was a significant inverse relation between the percent change in diastolic pressure and the initial plasma renin activity ($r = -0.77$, $p < 0.005$).[20]

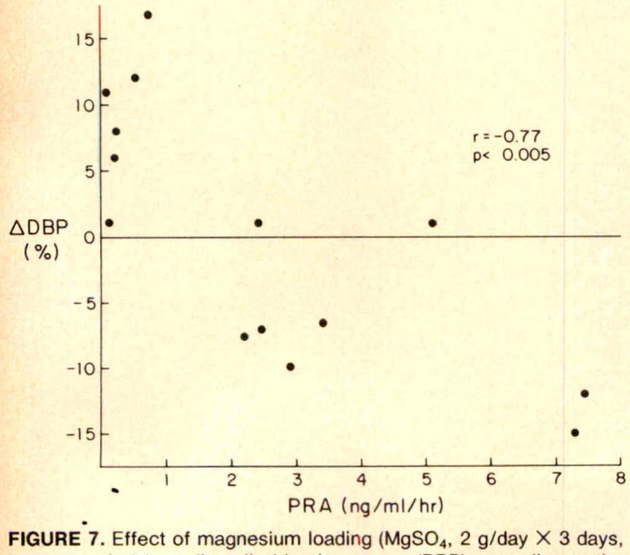

FIGURE 7. Effect of magnesium loading ($MgSO_4$, 2 g/day × 3 days, intramuscularly) on diastolic blood pressure (DBP) according to the initial plasma renin activity (PRA) in essential hypertensive subjects (data from reference 20).

Clinical Heterogeneity of Hypertension—Drug Therapy

While restriction of dietary sodium intake and, perhaps in the near future, calcium or magnesium supplementation may be initial maneuvers to benefit selected renin- or Ca^{++}-targeted subgroups of patients with mild to moderate hypertension, drug therapy still occupies a central position in the therapy of hypertension. Thus, it is of practical importance as well as of physiologic interest to ascertain whether measurement of plasma renin activity, serum Ca^{++} or other calcium metabolic indexes can similarly target subgroups of hypertensive patients who might preferentially benefit from specific drug classes. Indeed, historically, it has been the success of renin-sodium profiling in determining the blood pressure sensitivity to a variety of antihypertensive drugs that spurred continued research of renin system physiology and the utility of the vasoconstriction-volume analysis of hypertension.

Drugs and high-renin hypertension—beta blockers and converting enzyme inhibitors: Although the hypotensive effects of β-blocking drugs have long been established, the mechanism by which they exert their antihypertensive effects remains incompletely understood. Different observers have sug-

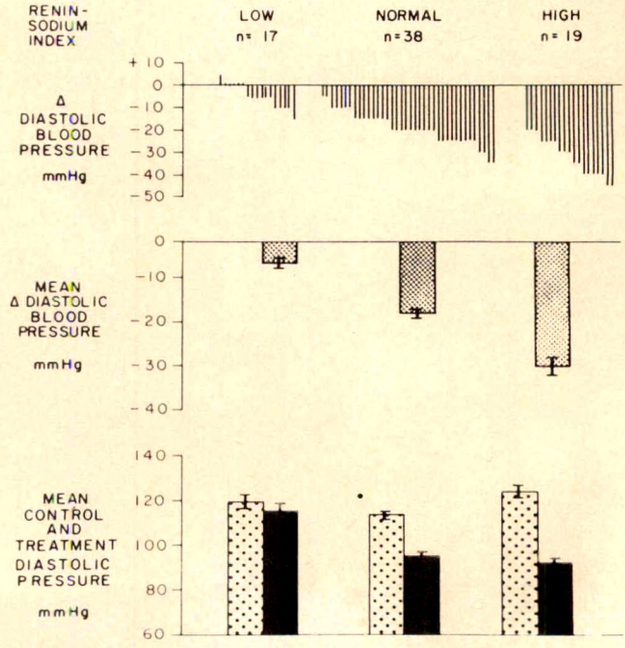

FIGURE 8. Hypotensive effects of β-adrenergic blockade in essential hypertensive patients grouped according to their renin-sodium profile. Reproduced with permission from N Engl J Med.[24]

TABLE III The Selective Effectiveness of Antihypertensive Drugs

Beta Blockers Are Preferentially Effective in High and Normal Renin Patients	Diuretics Are Preferentially Effective in Low Renin Patients
Bühler et al, N Engl J Med 1972;287:1209	Crane et al, Am J Med Sci 1970;260:311
Bühler et al, Am J Cardiol 1973;32:511	Spark et al, Ann Intern Med 1971;75:831
Castenfors et al, Acta Med Scand 1973;193:189	Crane et al, Am J Med 1972;52:457
Bühler et al, Am J Cardiol 1975;36:652	Carey et al, Arch Intern Med 1972;130:849
Pettinger et al, N Engl J Med 1975;292:1214	Adlin et al, Arch Intern Med 1972;130:855
Karlberg et al, Am J Cardiol 1976;27:642	Vaughan et al, Am J Cardiol 1973;32:523
Hollifield et al, N Engl J Med 1976;295:68	Castenfors et al, Acta Med Scand 1974;193:189
Weidman et al, Klin Wochenschr 1976;54:765	Distler et al, Dtsch Med Wochenschr 1974;99:864
Menard et al, Am J Med 1976;60:886	Douglas et al, JAMA 1974;227:518
Stumpe et al, Am J Med 1976;60:853	Karlberg et al, Am J Cardiol 1976;37:642
MacGregor et al, Clin Sci Mol Med 1976;50:18	MacGregor et al, Clin Sci Mol Med 1976;50:18
Boerth, Pediatr Res 1976;10:328	
Moore et al, Lancet 1976;2:67	
Bahr et al, Clin Pharmacol Ther 1976;20:130	
Zech et al, Postgrad Med J 1977;53:suppl 3:134	
Philipp et al, Dtsch Med Wochenschr 1977;102:569	
Beta Blockers Can Actually Raise Pressure in Low Renin Patients	**Diuretics Can Actually Raise Pressure in High Renin Patients**
Drayer et al, Am J Med 1976;60:897	Baer et al, Ann Intern Med 1977;86:257

gested primary cardiovascular actions, central nervous system effects and inhibition of renin secretion as alternative hypotheses, and evidence exists for each hypothesis.[21] However, cardiac indices are themselves incapable of predicting the blood pressure response to β blockers, and subjects in whom pressure is lowered, unchanged or even elevated by these drugs may experience equivalent effects on, for example, cardiac output.[22] Similarly, at doses that have widely different capacities to penetrate the central nervous system, these agents show an equivalent ability to lower blood pressure.[23] On the other hand, evaluation of renin system activity does indicate that those patients most sensitive to β blockade are those with high ambient plasma renin activity, and that those with a low renin profile are insensitive to such therapy (Fig. 8).[24] With the recent development of drug therapy specifically designed to inhibit the renin-angiotensin system, such as converting enzyme inhibitors, the role of renin-mediated vasoconstriction in essential hypertension has been conclusively established. As with the blood pressure effects of β blockers, the hypotensive efficacy of an agent such as captopril is directly related to the initial plasma renin activity (Fig. 9).[25]

Thus, the physician who measures plasma renin activity in a given subject and finds it inappropriately elevated might consider initiating drug therapy with either β-blocking drugs or converting enzyme inhibitors. Further, the therapeutic implications of a high-renin profile apply even in the elderly, despite the decreased occurrence of high plasma renin activity in this population. Among elderly hypertensives, β blockers were shown to be preferentially effective in high renin subjects, while diuretics were more beneficial in lower renin subjects.[26,27]

Drugs and low renin hypertension—diuretics and calcium-channel blockers: According to the vasoconstriction-volume analysis of hypertension, those hypertensive subjects in whom plasma renin activity is suppressed would be predicted to be more volume sensitive and thus more sensitive to diuretic agents. Evidence that supports this has been reported by us and others (Table III). Thus, in choosing drug therapy, diuretics might be most reasonably considered in low renin hypertensive subjects.

In addition to diuretics, calcium-channel blocking agents have also emerged as selectively beneficial in low renin subjects; this has been shown thus far for both verapamil and nifedipine.[28] This selective benefit of calcium-channel blockade in low renin, volume-de-

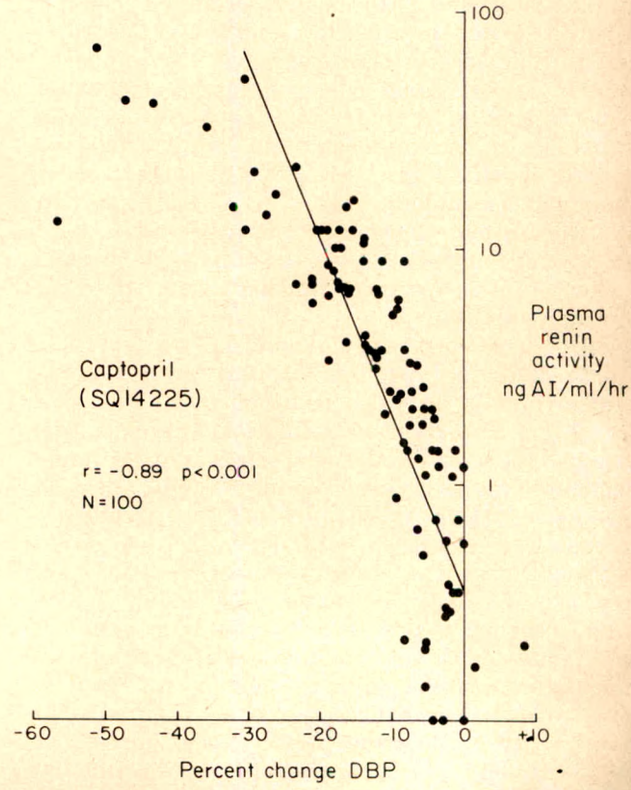

FIGURE 9. Hypotensive effects of converting enzyme blockade with captopril in relation to the initial plasma renin activity (cited in reference 25). DBP = diastolic blood pressure.

pendent hypertensive states has also been established in a variety of animal models and may indicate a greater dependence of hypertension on extracellular calcium in this form of hypertensive disease.[29,30] It may also reflect the lower serum Ca^{++} and higher magnesium levels characteristic of low renin hypertension. This ionic profile itself enhances the efficacy of calcium-channel blockade, as opposed to higher renin forms of hypertension, in which the observed higher serum Ca^{++} and lower magnesium levels would be expected to blunt calcium-channel antagonism.[31]

The Renin System, Calcium Metabolism and Rational Choice of Antihypertensive Therapy

On the basis of this discussion, it appears that renin-sodium profiling can provide a practical basis for therapeutic choices in hypertension. Moreover, recent knowledge linking calcium metabolism and renin system activity lends further significance to these choices. A consistent pattern is emerging, in which the initial deviations in serum Ca^{++} and magnesium observed among the different renin subgroups of hypertensives are such that maneuvers that exacerbate these deviations also exacerbate the hypertension. Similarly, successful dietary or drug therapy tends to reverse these ionic deviations and to reverse the hypertension.

Thus, high dietary salt intake exacerbates blood pressure in exactly those patients in whom serum Ca^{++} is most suppressed—those with a lower renin, lower Ca^{++} profile. Conversely, restriction of sodium intake, associated with higher serum Ca^{++} levels, benefits the salt-sensitive, low renin, lower Ca^{++} individual. Similarly, calcium supplementation is most beneficial in the same low renin, lower calcium subjects. Interestingly, these subjects also have higher initial levels of serum magnesium (as previously discussed), which calcium therapy lowers.[20] On the other hand, magnesium lowers serum Ca^{++} levels, can actually worsen hypertension in the lower renin, lower Ca^{++} person and is most beneficial in the high-renin, higher serum Ca^{++} subject, who has lower initial levels of magnesium.[20]

This parallel between the ionic and blood pressure effects of dietary sodium, calcium and magnesium supplements is now also being observed with drug therapy of hypertension. Diuretics have long been known to be capable of raising serum calcium values, while lowering levels of serum magnesium. The calcium-channel blocker, nifedipine, selectively beneficial in exactly the same type of hypertensive—the low renin, lower calcium subject—also raises Ca^{++} and lowers magnesium.[32] Thus, it is possible that diet and drug therapy may possess a common basis of action-reversing ionic deviations of circulating calcium and magnesium, as reflected by the ambient plasma renin activity. How these deviations are linked to renin system activity and how they relate to the abnormal intracellular levels of both cytosolic free calcium and free magnesium recently described[33,34] are currently unknown and afford exciting challenges for future research.

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The Evolution of Antihypertensive Therapy

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Beginning in the early 1950s, when a ganglioplegic agent and a vasodilator were used in combination to provide long-term control of severe hypertension, which neither drug alone could control, much has been learned about the management of hypertension from the use of new antihypertensive agents in man and from clinical trials of antihypertensive regimens. Some of this information includes: (1) the unexpected yet very real hazards as well as benefits associated with the long-term use of powerful drugs, in particular the original description of hydralazine-induced lupus, its relation to genetic markers and its association with control of hypertension; (2) the apparently decreasing need for antihypertensive drugs in subjects with well-controlled severe and moderate hypertension; (3) the identification of risk factors for the complications of hypertension and the quantitation of their effects; (4) the decrease in the incidence of hypertensive complications associated with the pharmacologic treatment of severe, moderate and, at least, the upper ranges of mild hypertension; (5) the possibility of designing a chemical to block a specific reaction and the realization that it would have broader than expected effects; and (6) the primary prevention of myocardial infarction in very high risk subjects.

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The first real success in treating essential hypertension occurred about 50 years ago with the advent of surgical sympathectomy. Early treatment was uncertain, hazardous and unpleasant in the extreme; however, it held out hope for the future because it demonstrated that control was possible. In contrast, today virtually all essential hypertension can be controlled with relatively little difficulty. Although we still do not know the underlying mechanisms involved in maintaining an elevated blood pressure, many of the advances in the management of hypertension have provided important information. It seems timely to review what has been learned from the use of antihypertensive agents in man and from clinical trials of antihypertensive treatment. The marked decrease in the severity of hypertension in the United States (particularly in whites) during the last 30 years has dramatically shifted the emphasis from the treatment of malignant hypertension to the treatment of mild hypertension.

I would like to set the stage for my discussion by quoting some comments about the early treatment of hypertension made by E. Weiss in 1939:

> What has been done in an effort to reduce the blood pressure? Because of all ill-founded idea that protein was responsible for hypertension and kidney disease, the patient was denied meat and eggs, and especially red meat, which for some reason was looked upon with particular dread. His diet was rendered even more unpalatable by the withdrawal of salt. Sympathy would doubtless have been extended to this half-starved fellow except that he probably was not able to eat anyway, his teeth having been extracted on the theory that focal infection had something to do with hypertension. Even before this he had sacrificed his tonsils and had had his sinuses punctured because of the same theory. In case some food had been consumed, the slight colonic residue was promptly washed out by numerous colonic irrigations, especially during the period when the theory of auto-intoxication was enjoying a wave of popularity. To add to his unhappiness he was often told to stop work and exercise. Of course, he was denied alcohol and tobacco as well as coffee and tea, and as a climax to the difficulties of this unfortunate person, he may now fall in the clutches of the neurosurgeon, who is prepared to separate him from his sympathetic nervous system.[1]

This quotation reflects the desperate measures taken by physicians to treat a rapidly fatal disease for which no effective treatment had yet been developed.

Even before the introduction of effective drug therapy, some drugs were known to lower blood pressure acutely but transiently. Papaverine was the first such drug used to treat hypertension, followed by sodium nitroprusside and nitroglycerin.[2] Sodium nitroprus-

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TABLE I Advances in Managing Hypertension and Major Findings

Year	Drug	Study	Significant Observation
1951	C_6 + hydralazine		Control of severe hypertension with 2 differently acting agents
1953	Hydralazine		Remissions associated with "toxic" autoimmune response
1955	Hydralazine		Hypertension controlled by "metal binders" and induced by cadmium and lead
1955	Chlorothiazide		Diuretics potentiate other antihypertensive agents
1956	C_6 + hydralazine		Remissions and partial remissions accompanying good control
1959		Framingham	Natural history of untreated hypertension and risk factor concept
1967 and 1970		VA study III	Benefit from treating severe and moderate hypertension
1972		VA study III	Same benefit for treating diastolic pressures in 70, 80 and 90-mm Hg range
1975	Captopril		Efficacy of designed converting enzyme inhibitor
1977		VA–NIH trial	Thiazide-induced increase in cholesterol
1979		HDFP	Possible benefit from treating mild hypertension to the mid80-mm Hg range
1979	Calcium antagonists		Cellular mechanism of vasodilatation
1980		ANBPS	Benefit from treating diastolic pressures of 95 to 110 mm Hg
1981		BMIS and BHAT	(Primary prevention of myocardial infarction)
1983		MRFIT	Possible drug-specific differences in benefit from treatment
1984		LRC trial	(Decrease in myocardial infarction by lowering cholesterol levels above 265 mg%)
1984		SHEP I	Control of isolated systolic hypertension by diuretics

Important observations were initially made as the result of new antihypertensive drugs and then as a result of multicenter trials. The dates approximate the time when the observations were made or published. The parentheses indicate studies that dealt with atherosclerosis; they are included because myocardial infarction is a major complication of hypertension. See text.

side was recognized by Johnson in 1929 as a very effective vasodilator.[3] Although it was tested as an antihypertensive agent, it was impractical therapeutically at that time because of its short duration of action, its unstable shelf life and the requirement that it be administered parenterally. In the 1930s and 1940s, before oral drugs capable of providing long-term control became available, surgical sympathectomy[4] and, subsequently, a very rigid low-sodium, high-potassium diet[5] controlled hypertension to some extent, indicating that the sympathetic nervous system and electrolytes were involved in the maintenance of an elevated blood pressure. Some of the important lessons subsequently learned from the use of new antihypertensive agents in man and from clinical trials of antihypertensive treatment are listed in Table I.

Long-Term Control of Severe Hypertension with Two Differently Acting Drugs

Modern pharmacologic therapy of hypertension had its beginning in the late 1940s, when routine screening for an antihypertensive effect identified the antituberculous hydrazine as a vasodilator and when 5- and 6-carbon methonium compounds were recognized as effective ganglioplegic agents.[6] Neither hydralazine nor the methonium compounds alone could do more than provide transient control of blood pressure. However, in 1951 Schroeder demonstrated that they could provide long-term control when administered together.[7] For the first time, patients with malignant hypertension had their blood pressure controlled and their rapidly progressive disease process abruptly halted. One of the patients in this initial group of 4 survived more than 10 years and another more than 20 years. Because the median survival time for untreated "malignant hypertension" was less than half a year,[8] it did not take long to demonstrate that therapy prolonged life. There were major problems in controlling blood pressure with these primitive drugs and in patient acceptance, but it had been clearly demonstrated that *attacking 2 different aspects of hypertension with 2 different drugs worked when neither one alone could provide long-term control.* These early antihypertensive agents were powerful but dangerous. Several years were needed to learn to use them effectively, during which time major and unexpected adverse effects appeared.

Good Hypertension Control and Both "Partial" and Complete Remission

Hypertensive patients with well-controlled blood pressure show a decreasing need for antihypertensive drugs, an effect currently being examined by various "step-down" studies. In the extreme case, this process leads to persistent normotension without drugs. The phenomenon was first reported in 1956;[9] it was not limited to a few unusual patients, but was a general characteristic of the entire hypertensive population in which diastolic pressure was adequately controlled by treatment. The report considered 114 moderately and severely hypertensive patients, all of whom took blood pressure readings at home. One month after hospital discharge, 79 were controlled (mean diastolic pressure at home <100 mm Hg) and 35 were uncontrolled. A year later, the mean diastolic pressure of the controlled patients had decreased slightly, and their intakes of hexamethonium and hydralazine had decreased to 74% and 89%, respectively, of their intake at 1 month after discharge. The mean diastolic pressure of the uncontrolled patients had increased slightly, and they were ingesting 97% and 98%, respectively, of their initial doses of the 2 drugs. After 3 years of treatment, the controlled group was slightly better controlled and needed an average of only 50% of their 1-month doses, while the uncontrolled group was no better controlled and was taking almost 80% of their 1-month doses. As those who have used these drugs know, the dosage range required for control is narrow, so this decrease in dosage for controlled patients was significant. *Thus, good control of blood pressure can lead to a lessening of the requirement for antihypertensive drugs.*

In a few patients, the phenomenon of diminishing drug requirements continued until complete discon-

tinuation of antihypertensive drugs was possible. In the 1956 report, "complete remissions"—normotension with no antihypertensive medicine—were reported in 10 of 114 patients.[9] Their pretreatment diastolic pressure ranged from 113 to 146 mm Hg. In 1966, 8 of these remissions were reported to have persisted for more than 10 years, although 3 patients noted the occasional use of diuretic or reserpine under "stress."[10] *Thus, long-term remissions were seen in 8 of 79 well-controlled patients.*

Hydralazine

The mechanism of action of this drug has never been clearly delineated beyond that it is a peripheral vasodilator that acts directly on vascular smooth muscle. Chemically, hydralazine is very reactive. In addition, it is a strong binding agent for certain metals. Metal binding is a property shared with other early vasodilators: nitroprusside, azide, thiocyanate and some experimental vasopressor mercaptans and pyrophosphates.

Hydralazine's ability to bind certain metals may or may not be important, but I mention it for 3 reasons: (1) because the patients treated with large doses of hydralazine were the ones who had remissions, and their clinical courses raised the possibility of depletion of an essential nutrient; (2) because of the possible competition between calcium and some of the metals bound by hydralazine and calcium; and (3) because of the recent report of a strong positive correlation between blood lead and blood pressure levels in the National Health and Nutrition Examination Survey sample of the U.S. population—in which a negative correlation with zinc raised the possibility of cadmium involvement.[11]

Because of the chelating properties of vasodilators, the effect of EDTA was tested in hypertensive animals. A dramatic antihypertensive effect was observed.[12] This led to the recognition that 2 ubiquitous nonessential trace metals, cadmium and lead, could induce something resembling human essential hypertension in rats. The doses required to induce hypertension were small and comparable to human *environmental* exposures.[13] Large body burdens of these 2 divalent metals in man might be expected to compete with calcium. Thus, cadmium and lead are possible contributors to human hypertension. The recently observed correlations from the National Health and Nutrition Examination Survey suggest further investigation.

Toxicity

The first 4 clinically effective antihypertensive agents produced major and unexpected toxic manifestations, emphasizing that long-term exposure to a drug with important effects on vital biologic functions is liable to produce unwanted effects as well. Hydralazine toxicity was the first to be recognized. This drug induced an autoimmune lupus-like syndrome in as much as 10% of the exposed population. The incidence was related to the extent of exposure in the susceptible portion of the population. Confined to genetically controlled "slow acetylators"[14] and almost exclusively to whites, this syndrome was of particular interest because its only recognized prodrome was normotension, which almost always persisted during the toxic phase and usually until symptoms had remitted.[15] For some toxic patients, this normotension developed into complete asymptomatic remission that persisted into the posttoxic period when patients were entirely asymptomatic and apparently well.[14] The remissions associated with autoimmune toxicity to hydralazine were different from, and not to be confused with, the previously described remissions associated with good control of pressure and the associated gradual decrease in medications. Under certain conditions (prolonged low hydralazine exposure after symptoms appeared), the remission rate in toxic patients approximated 50%.[16]

Hexamethonium, a ganglioplegic agent, was initially assumed to have no effect other than inhibition of all autonomic function, making life miserable for the patient, but in the process lowering his or her blood pressure. Hexamethonium, however, induced a fatal fibrinous pneumonitis characterized by extreme tachypnea without other symptoms in patients with malignant hypertension that had progressed to minimal azotemia.[17] This catastrophic response is still unexplained, but it does not evoke great concern, because hexamethonium is no longer used.

The use of reserpine, the third type of effective antihypertensive drug to become available, showed that a prompt effect can be forced from a long-acting drug, but that the very large doses needed to do so brought major toxic effects as the drug accumulated. Before this was recognized, doses from 10 to 100 times larger than the largest oral doses recommended today (2.5 to 25 mg/day) were prescribed and caused major depression in many patients, requiring prolonged hospitalization in closed wards.[18,19] Remembering these early psychoses, some physicians still hesitate to use reserpine. In today's doses, however, the drug is an effective adrenergic blocking agent, and its uniquely long half-life can be very helpful for patients who have difficulty remembering to take their medication. Although reserpine is usually characterized as a relatively weak antihypertensive agent, in head-to-head comparisons with other adrenergic blocking agents, it has always proved as good as, or better than, the competition. Because it is long-acting and is usually given in excess (the usual daily dose is 0.25 mg, but 0.05 mg provides 80% of the antihypertensive effect), 1 or 2 doses a week can provide a continuous antihypertensive effect. No other currently available agent, except perhaps guanethidine, is comparably long-acting.

Chlorothiazide became available in the mid1950s. Alone, it is a weak antihypertensive agent that has little effect on severe hypertension. Chlorothiazide and related thiazides, do, however, markedly potentiate the antihypertensive effect of most other antihypertensive drugs and, in so doing, serve the very important function of decreasing adverse effects. Initially, thiazide was considered to be without significant toxicity, which may very well be true; however, there is a recent suspicion that under certain ill-defined condi-

TABLE II Summary of Results from Veterans Administration Study[24,26,36]

Total Patients (treated and placebo)	Severity of Hypertension	Placebo Patients: Events/100 Patient Years	Treated Patients: Events/100 Patient Years	Ratio of Hypertensive to Arteriosclerotic Events	Therapeutic Efficacy Ratio
73	Severe (>115 mm Hg)	23	1.6	2.1	14
110	Moderate (105–114 mm Hg)	11	1.3	1.2	8.5
84	Mild (90–104 mm Hg)	9.3	4.7	1.1	2.0*

* Events that are not appropriately classified as either hypertensive or arteriosclerotic have been excluded, thus modifying the number of events and the therapeutic efficacy ratios slightly. The more rigidly derived therapeutic efficacy ratio, including all events, is only 1.5 for mild hypertensive subjects.

The randomization process rendered the treated and untreated populations very similar in age, race and other characteristics. The last 4 columns indicate frequencies of events as functions of the severity of hypertension for patients on placebo or active drugs, the ratio of hypertensive to arteriosclerotic events and the ratio of the event rate for placebo patients divided by the event rate for patients on an active drug.

tions, its long-term use may dangerously deplete the body stores of potassium and thereby induce fatal arrhythmia in rare susceptible patients. At present the possibility that thiazides actually have this toxic capability is nothing more than a suspicion; there is no proof.

In addition to the possibility of rare but catastrophic toxicity, there is recent concern regarding wrong-way chemical changes associated with thiazides. In 1976, the Veterans Administration–National Institutes of Health Mild Hypertension Feasibility Trial was the first double-blind, placebo-controlled study to confirm the suspected thiazide-induced increase in total cholesterol level.[20,21] The observed effect was not large, and there is a real question about its clinical significance. The increase during thiazide treatment averaged 5% from a pretreatment level of 200 mg%; it was greater for those with a lower pretreatment level and therefore for younger patients. The effect seemed to persist with little change for at least 2 years. Unfortunately, the increase did not include high-density lipoprotein cholesterol. Since this observation was made the effects of other antihypertensive agents on cholesterol have been studied in smaller series of patients. The reports are inconsistent, but a variety of agents has been observed to induce similar slight increases in cholesterol.[22] Hydralazine, in contrast to most other antihypertensive agents, significantly and consistently lowers circulating cholesterol, and the effect is sometimes much larger than the thiazide effect.[23] In addition to increasing total cholesterol by about 10 mg%, thiazide has also been observed to increase blood glucose by an average of 4.7 mg% and uric acid by an average of 1.4 mg%, and to decrease potassium by an average of 0.56 mEq/liter.[24] *There is no evidence, however, that any of these chemical effects is associated with an adverse clinical effect.*

The Framingham Study and Risk Factors

In addition to what has been learned from antihypertensive agents, epidemiologic studies have added greatly to our understanding of the hypertensive process. The Framingham study[25] provides our most useful insight into the natural history of untreated cardiovascular disease. Almost 6,000 inhabitants of Framingham, Massachusetts, enrolled in this study and were evaluated initially and then reevaluated biannually for various cardiovascular risk factors. From this come our best data on the incidence of hypertensive and atherosclerotic complications, particularly myocardial infarction and stroke, as functions of what are now designated "risk factors". For a 50-year-old white man, the risk of myocardial infarction can vary by as much as 20-fold, depending on the presence or absence of 6 risk factors. *Thus, the Framingham study quantitated the effect of common risk factors.*

Veterans Administration Study of the Benefits of Antihypertensive Treatment

The next major advance came in 1970, with the report of a randomized, double-blind, placebo-controlled study showing that treatment lowered morbidity and mortality for patients with diastolic pressure ≥105 mm Hg.[26] This report dramatically changed our whole way of thinking about hypertension; before 1970, many physicians were not enthusiastic about treating hypertension, because there was no proof of benefit. After 1970, *effective treatment was considered mandatory for a patient with diastolic pressure ≥105 mm Hg.*

This Veterans Administration study makes a number of other points; Table II presents the data for some of them. First, not unexpectedly, the untreated severely hypertensive patients had twice as many hypertensive events as atherosclerotic events, whereas the untreated mild hypertensive patients had equal numbers of hypertensive and atherosclerotic events. Second, without treatment, the morbid-event rate for the veteran population involved ranged from 23/100 patient years for severe hypertension to 9.3 for mild hypertension. Third, with treatment, the comparable-event rates were 1.6 and 4.7 for severe and mild hypertension, respectively. (The event rate for treated patients was higher for the mild hypertensive than for the severe hypertensive patients.) Finally, the "therapeutic efficacy ratio" ranged from 14 for severe hypertensives to 2 for mild hyertensives. Even with the small number of patients, "14" is obviously statistically significant, and so is "8.5" for moderate hypertension; however, "2" is not even close to being a significant value.

Goal diastolic pressure: One other observation of great potential significance emerged from this study. It has been generally assumed that the lower the treated diastolic pressure, the greater the benefit of treatment. For the treated veterans in this study, however,

there was no relation between the degree of blood pressure control and the decrease in morbid events. Thus, partial control of diastolic pressure was just as good as maximal control. Approximately one-third of the actively treated patients had average treated diastolic pressures in the 70-mm Hg range, one-third in the 80-mm Hg range and one-third in the 90-mm Hg range. The annual morbid-event rate was 12% for the entire treated group and 12% for each of these 3 subgroups.[27] In contrast, the annual morbid-event rate was 27% for the entire group of placebo-treated patients. Because the pretreatment diastolic pressures were similar for the 3 subgroups of actively treated patients, treatment produced an average fall in diastolic pressure of 27 mm Hg for the best controlled one-third compared with only 7 mm Hg for the worst controlled one-third of patients. Yet these 2 very different falls in diastolic pressure were associated with the same morbid-event rate. *This small data set suggests that nearly maximal benefit is attained with partial control.* Alternatively, it is consistent with the "Multiple Risk Factor Intervention Trial (MRFIT) anomaly."[28]

Primary Prevention of Myocardial Infarction

Although by definition primary prevention of myocardial infarction is distinct from treatment of hypertension, the goal is obviously the same for both therapeutic maneuvers. The British Practolol Study, which was discontinued because of serious toxicity, suggested that there was benefit from β blockade and that it was unrelated to the antihypertensive effect, because it was limited to the normotensive cohort.[29] The Norwegian Beta-Blocker Myocardial Infarction Study was the first to demonstrate clear protection against a *second* myocardial infarct, i.e., protection in very high risk patients. The difference in mortality between treatment and placebo appeared promptly and seemed to persist through the second year; the reduction in mortality with 33 months of treatment was 45%.[30] Aside from a higher baseline rate of myocardial infarction and shorter persistence of the beneficial effect, the subsequent Beta-Blocker Heart Attack Trial in the U.S. and Canada produced a similar result.[31]

The Coronary Primary Prevention Trial of the Lipid Research Clinics demonstrated that for middle-aged men with cholesterol levels above 265 mg% (the highest 5% of those with type II hyperlipoproteinemia), the cholesterol-lowering drug cholestyramine decreased cardiovascular mortality;[32] however, the extent to which this result can be extrapolated to other groups, including those with lower cholesterol levels, remains uncertain. *Thus, at minimum, it is reasonable to emphasize β blockade in lowering the blood pressure of hypertensive patients who are at high risk for myocardial infarction and to use cholesterol-lowering measures for those with very high levels.*[32]

The Benefits of Treating Mild Hypertension

The Hypertension Detection and Follow-up Program (HDFP) was initiated shortly after the 1970 report of the Veterans Administration study; the goal was to determine whether intensive treatment of hypertension by special therapists with nearly unlimited funds and time could lower mortality more than "regular treatment," which at that time was generally not intensive.[33] *The HDFP was, therefore, not a double-blind study of treatment versus no treatment.* Nonetheless, its results have been accepted by some as demonstrating great benefit by lowering the diastolic pressure of mildly hypertensive patients to the low 80-mm Hg range. The unusual design of HDFP and some of its unexplained findings raise questions about this interpretation. A 25% decrease in mortality between a special case group with average diastolic pressure of 83.4 mm Hg and a regular care group with diastolic pressure of 87.8 mm Hg is much greater than has ever been suggested by any other data. It is also much greater than HDFP observed in patients with moderate and severe hypertension; in them, regular care was actually better for moderately and severely hypertensive white women and for severely hypertensive white men. In addition to this unexpected result, HDFP had more than twice the mortality of 4 other studies with which a World Health Organization Expert Committee compared it;[34] this unexplainedly high mortality rate might have altered the blood pressure effect.

The similarly designed MRFIT failed to confirm the HDFP benefit in mild hypertension and raised some questions of its own.[28] In particular, the failure to demonstrate benefit raised the question of deleterious effects from intensive treatment. A MRFIT cohort of mild hypertensive subjects with electrocardiographic abnormalities was responsible for an excess of sudden deaths; it was this observation that first suggested that diuretic-induced hypokalemia *might* set the stage for fatal arrhythmia and sudden death in subjects with preexisting cardiac damage.

In contrast to HDFP and MRFIT, the Australian National Blood Pressure Study was a randomized, double-blind, placebo-controlled trial that demonstrated benefit from controlling pretreatment diastolic pressures of 95 to 110 mm Hg; it did not accept subjects with diastolic pressures <95 mm Hg, and so does not contribute information on the benefit of treating such patients.[35] In sharp contrast to HFDP, the Australian study observed little or no benefit from lowering the diastolic pressure of those subjects it did treat to <95 mm Hg. *Thus, although HDFP seemed to suggest benefit from lowering the diastolic pressure into the low 80-mm Hg range, the general trend of MRFIT and the Australian study suggests that treatment is not demonstrably helpful for subjects with diastolic pressures <95 mm Hg.*

Designed Drugs

Captopril was designed to inhibit the converting enzyme that splits angiotensin I into angiotensin II.[36] Its use demonstrated the therapeutic efficacy of a specifically designed enzyme inhibitor; however, it too raised some questions. Its antihypertensive effect was much more widespread than anticipated. It has been unexpectedly effective in low renin states when angiotensin II is apparently not involved in the maintenance of hypertension. It has been suggested, as a

partial explanation, that inhibiting the converting enzyme protects the vasodepressor nonapeptide, bradykinin.

Systolic Hypertension in the Elderly

Although the Framingham study suggested that systolic pressure is as good as or better than diastolic pressure in predicting cardiovascular complications, treatment of isolated systolic hypertension, which is so common in the "elderly", has only recently been seriously considered. Isolated systolic hypertension appears in persons in their mid50s; by age 75 or 80, it involves one-fourth of the population. A recent feasibility trial, Systolic Hypertension in the Elderly Program (SHEP), addressed the practicality of a randomized, double-blind, placebo-controlled trial to determine whether treating isolated systolic hypertension would diminish morbidity and mortality and whether such treatment would influence the incidence of dementia and depression, a major problem in that age group. The feasibility trial determined that isolated systolic hypertension could be easily controlled, usually with thiazides alone, and that there were no significant problems associated with treatment.[37] Practicality having been demonstrated, a full-scale SHEP is just beginning. *Thus, although no recommendations can be made at the moment, it seems likely that blood pressure can be lowered in the elderly and that there is no obvious danger in treating isolated systolic hypertension in this group; moreover, a definite answer on the advantages of such treatment will be available in a few years.*

Calcium Antagonists

The most recent entrant into the field of antihypertensive agents—the calcium antagonists—holds great promise for the future. They attack the fundamental defect in hypertension—and, for the first time, we have some ideas as to how such agents might act. As to their eventual place in the antihypertensive armamentarium, we can only speculate at present, although theory suggests that it will be important.[38]

In summary, we have learned a lot and, in the process, have observed some major changes in a common underlying disease process and its treatment. We have watched malignant hypertension virtually disappear and mild hypertension replace it as the focus of our attention. We have watched the rates of myocardial infarction and stroke decrease. Now we must work at cure and, subsequently, on prevention. We have some evidence that both of these are possible, and some clues are beginning to emerge to suggest how we might approach the problem.

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Age, Race, Blood Pressure and Renin: Predictors for Antihypertensive Treatment with Calcium Antagonists

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Age, race, pretreatment blood pressure and plasma renin activity have been related to the antihypertensive response to calcium antagonists in studies that included 215 patients with mild to moderate essential hypertension. Adverse effects necessitated withdrawal from therapy in about 10% of the patients. All calcium antagonists lowered blood pressure significantly and comparably without weight gain or reflex tachycardia. In a multiple linear regression analysis of 138 white patients, age, pretreatment blood pressure and renin activity were of independent and significant predictive value for the antihypertensive response. Stratification of patients into 3 age groups disclosed a greater effect in patients older than 60 years compared with those between 40 and 60 years and those below 40 years, respectively ($p < 0.01$). In 16 middle-aged black patients, antihypertensive therapy with a calcium antagonist proved highly efficacious. Monotherapy with a calcium antagonist may become a first-line treatment for essential hypertension, particularly in older patients who have low renin activity and possibly in black patients as well.

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For more than 20 years calcium antagonists have been known to lower high blood pressure,[1,2] but their usefulness for the treatment of clinical hypertension has been recognized only recently.[3,4] Their introduction into a treatment regimen for hypertension affords the advantage of the good safety record that these drugs have acquired in the treatment of ischemic and hypertrophic obstructive heart disease as well as supraventricular arrhythmias. Calcium antagonists lower blood pressure by reducing elevated systemic vascular resistance.[3,5] It has been postulated that these drugs might specifically influence a deranged calcium entry–dependent, cellular vasoconstrictor mechanism in hypertension.[6,7] Clinically, calcium antagonists are most effective in older patients who often have low plasma renin activity.[4] However, the number of patients studied so far may not allow a generalization of these findings, and the relative impact of these factors is not clear because they are interrelated. In the present analysis we reexamined the predictive value of age, pretreatment blood pressure and plasma renin activity for the antihypertensive response to calcium antagonist monotherapy in patients with essential hypertension. Because the incidence of low renin hypertension is known to be high in blacks,[8] we also investigated the antihypertensive efficacy of calcium antagonist therapy in black African patients. We then compared the antihypertensive potentials of various calcium antagonists.

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Patients and Methods

Predictors of antihypertensive response: One hundred and fifty-three patients with essential hypertension (60 women and 93 men, ranging in age from 18 to 85 years, mean age 42.2) from the Basel Hypertension Clinic participated in this prospective, placebo-controlled study. Previously untreated patients (n = 40) received placebo tablets 2 times a day for 2 weeks. In patients who were already receiving therapy, treatment was discontinued and placebo tablets were given 2 times a day for 3 to 4 weeks. At the end of the placebo period, diastolic blood pressure (Korotkoff V) was >100 mm Hg after 10 minutes in the seated position in all patients.

Plasma renin activity was measured simultaneously using a radioimmunoassay.[9] Blood pressure was measured with a standard mercury sphygmomanometer. Mean pressure was calculated as diastolic pressure plus one-third of the pulse pressure. Heart rate was counted from the radial pulse.

TABLE I Baseline Characteristics and Changes During Antihypertensive Therapy with Calcium Entry Blockers

	Nifedipine (n = 66)		Nitrendipine (n = 29)		Verapamil (n = 43)		All (n = 138)	
	Control	Change	Control	Change	Control	Change	Control	Change
Age (years)	52.2 ± 1.6		52.1 ± 2.0		52.9 ± 2.2		52.4 ± 1.0	
Blood pressure (mm Hg)								
Systolic	170 ± 2.5	−25.3 ± 2.5*	169 ± 2.3	−23.4 ± 2.8*	171 ± 2.5	−18.6 ± 3.1*	170 ± 1.4	−22.8 ± 1.1
Diastolic	106 ± 1.0	−17.8 ± 1.2*	107 ± 1.2	−16.8 ± 2.2*	108 ± 0.9	−14.9 ± 1.6*	107 ± 0.6	−16.7 ± 0.6
Mean	127 ± 1.2	−20.3 ± 1.5*	128 ± 1.4	−18.9 ± 2.2*	129 ± 1.2	−16.1 ± 1.9*	129 ± 0.7	−18.8 ± 1.0
Heart rate (beats/min)	76 ± 1.2	0.7 ± 1.2	78 ± 1.4	−0.4 ± 1.9	81 ± 1.3	−5.4 ± 1.1†	78 ± 0.5	−1.4 ± 0.4
Weight (kg)	81 ± 2.1	0.2 ± 0.4	77.9 ± 2.3	−0.7 ± 0.2	83 ± 4.0	0.3 ± 0.4	81.2 ± 2.4	0.1 ± 0.2

Values are mean ± standard error of the mean.
* $p < 0.01$.
† $p < 0.025$ for comparison of verapamil effects versus those of nifedipine and nitrendipine.

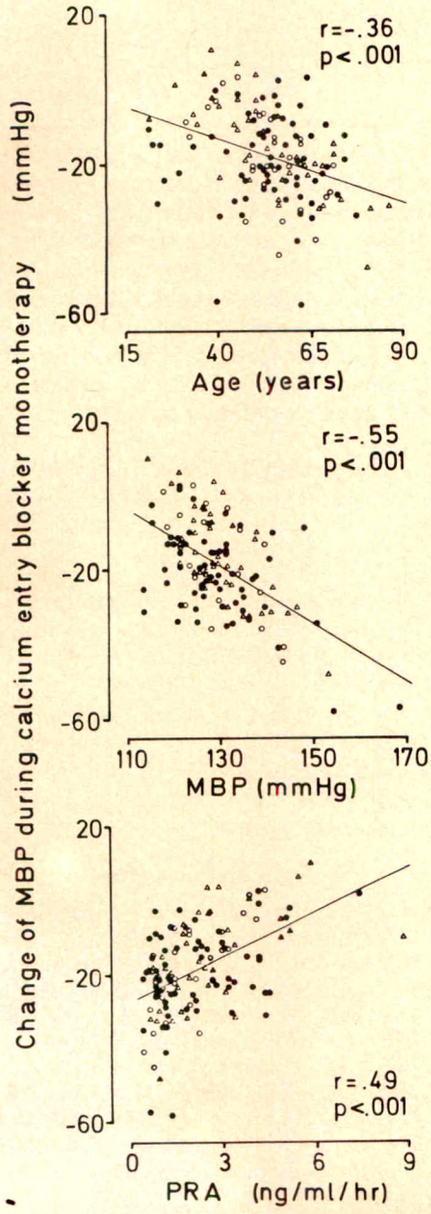

FIGURE 1. Linear relations between age, pretreatment plasma renin activity and blood pressure and antihypertensive response to calcium antagonists in essential hypertension. MBP = mean blood pressure; PRA = plasma renin activity; ● = nifedipine, n = 66; ○ = nitrendipine, n = 29; △ = verapamil, n = 43.

Antihypertensive effect, body weight and occurrence of adverse effects were assessed biweekly. If diastolic pressure remained >95 mm Hg, drug dosages were increased according to the therapeutic regimens that will be described.

Seventy-eight patients (50 men and 28 women, ranging in age from 21 to 76 years, mean age 42.6) received nifedipine in 20-mg tablets. Treatment was started with 20 mg, 2 times a day, and increased up to a maximum of 40 mg, 2 times a day. Treatment had to be discontinued within the first 4 weeks in 12 patients because of adverse effects. Therefore, 66 patients receiving an average dose of 52 mg/day for an average of 93 days were included in this analysis.

Thirty-one patients (20 men and 11 women, ranging in age from 29 to 70 years, mean age 53) received the dihydropyridine derivative nitrendipine; a starting dose of 20 mg, 2 times a day, was increased if needed to a maximum of 40 mg, 2 times a day. Two patients in this group had to be withdrawn in the first 4 weeks because of adverse effects. Thus, results from 29 patients who were treated with a mean dose of 35 mg/day for an average of 90 days were included in the statistical analysis.

Forty-four patients (23 men and 21 women, ranging in age from 20 to 85, mean age 53) were treated with verapamil given as a 120-mg, slow-release preparation.[4] Treatment was started with 120 mg, 2 times a day, and increased up to a maximum of 240 mg, 3 times a day. Treatment had to be discontinued after 2 weeks in 1 patient because of adverse effects. The remaining 43 patients were treated with an average dose of 427 mg/day for an average of 93 days.

Comparison of antihypertensive efficacy: The antihypertensive efficacy of various calcium antagonists was compared in 46 patients. Following a 2-week placebo period, patients were given 1 calcium antagonist for 3 months, followed by another 2-week placebo period. Next, a different calcium antagonist was prescribed for an additional 3 months. A comparison between verapamil (240 mg, 2 times day) and diltiazem (120 mg, 2 times a day) was made in 12 patients and between nitrendipine (20 mg, 2 times a day) and verapamil (240 mg, 2 times a day) in 15 patients. Tiapamil (600 mg, 2 times a day) and verapamil (240 mg, 2 times a day) were compared in 9 patients, and nitrendipine (20 mg, 2 times a day) and a new dihydropyridine derivative, PN 200-110 (Sandoz) (10 mg, 2 times a day), in 10 patients.

Race and antihypertensive efficacy: Sixteen black patients with essential hypertension from the Medifad Heart Center in Lagos, Nigeria (ranging in age from 37 to 59 years, mean age 48), were given placebo for 2 weeks followed by 20-mg nifedipine tablets 2 times a day for 6 weeks. Blood pressure was measured using a standard mercury sphygmomanometer with Korotkoff V taken as diastolic pressure. In these patients, blood pressure and heart rate were recorded in the supine position after 5 minutes of rest.

Statistical analysis: In order to analyze the impact of age, pretreatment blood pressure and plasma renin activity on the antihypertensive response to calcium antagonists in the first 153 patients, statistical evaluation was performed in the verapamil, nifedipine and nitrendipine groups separately and combined, using 1-way analysis of variance, paired and unpaired *t* tests, linear and multiple linear regression as well as χ^2 analysis. Intraindividual comparisons of the antihypertensive efficacy of the various calcium antagonists were performed by paired *t* test and linear regression analysis. Group statistics are shown as mean ± standard error of the mean as an index of dispersion.

Results

Age, renin and blood pressure as predictors of antihypertensive response: The 3 calcium antagonist treatment groups did not differ with respect to age and pretreatment characteristics (Table I). The effects of treatment in the 3 groups were comparable but heart rate decreased in verapamil-treated patients and remained unchanged in the others. Weight did not change in any group.

In an analysis of all patients, age and pretreatment blood pressure were directly related and plasma renin activity was inversely related to the antihypertensive effect of calcium antagonists (Fig. 1). Age and mean blood pressure were also inversely related to plasma renin activity ($r = -0.36$ and $r = -0.25$, $p < 0.01$ for both). A multiple linear regression analysis between age, pretreatment blood pressure and plasma renin activity as independent variables and the fall of mean blood pressure during long-term therapy showed a significant multiple linear correlation ($r = 0.49$, $p < 0.001$). All 3 variables had independent and significant effects on the antihypertensive response to calcium antagonists, with pretreatment blood pressure exhibiting the strongest influence ($F = 62.7$, $p < 0.01$) and plasma renin activity the weakest influence ($F = 18.2$, $p < 0.05$).

Although the linear correlation between age and response to calcium antagonists was rather weak (Fig. 1), older patients seemed to respond better to calcium entry blockers. When divided into 3 age groups, patients older than 60 years had, on the average, a greater blood pressure reduction compared with those between 40 and 60 years and those younger than 40 years ($p < 0.01$, analysis of variance). When considering a diastolic pressure <95 mm Hg during therapy as normal, 94% of patients older than 60 years normalized their blood pressure compared with 50% of middle-aged patients and 28% of younger patients ($p < 0.01$, χ^2).

Nifedipine caused adverse effects necessitating discontinuation of treatment in 12 patients within the first 4 weeks: 11 patients had flushing, severe headaches and migraine attacks and 1 patient had ankle edema. An additional 3 patients complained of headaches early during therapy and 7 patients noticed minor degrees of ankle edema. Verapamil monotherapy caused constipation in 5 patients, leading to withdrawal from therapy in 1. Nitrendipine was discontinued in 1 patient because of headache and ankle edema. Two other patients complained of hot legs, and 1 patient had a minor degree of ankle edema. There was no obvious relation between the occurrence of adverse effects and the patients' age or sex.

Intraindividual comparisons of different types of calcium antagonists: All calcium antagonists used in this study lowered blood pressure to a similar extent in the 4 crossover treatment groups. The comparability of their effects on blood pressure is further demonstrated by the close correlations observed between the reductions in blood pressure associated with the various drugs in these experiments (Fig. 2).

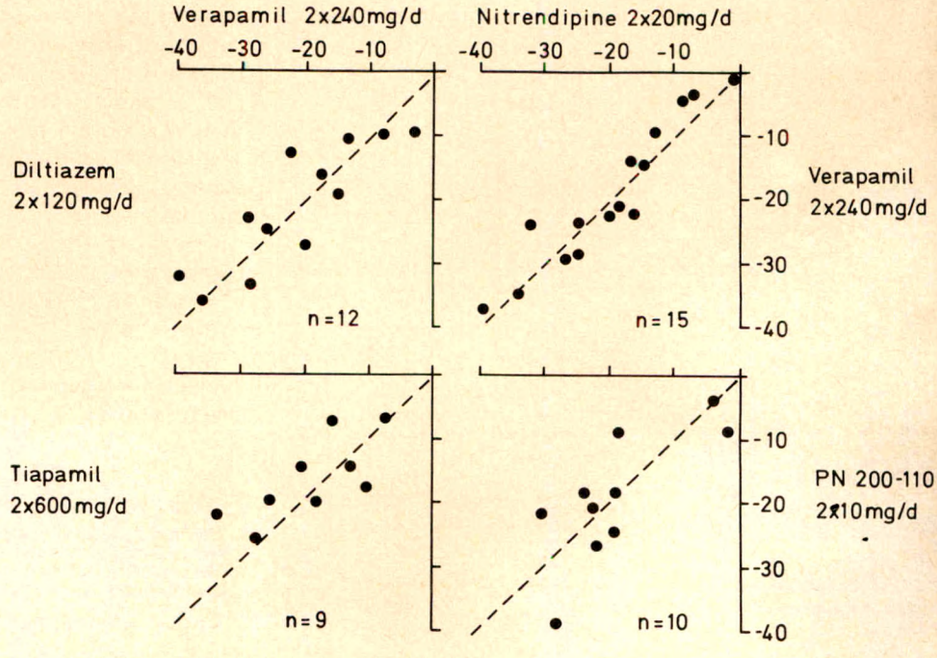

FIGURE 2. Blood pressure responses to various calcium antagonists in 4 groups of patients. Decreases of blood pressure observed with 1 compound were closely correlated with those observed after a crossover to a different drug.

Antihypertensive efficacy of nifedipine in black patients: Nifedipine was well tolerated in 16 black African patients. However, it was of interest that 5 patients reported polyuria as a minor adverse effect. As shown in Figure 3, blood pressure was reduced markedly and significantly (mean pressure 136.8 ± 2.2 vs 94.2 ± 1.39 mm Hg, $p < 0.001$) without significant changes in heart rate (75 ± 1.9 vs 79.9 ± 1.7) or weight (71.9 ± 3.1 vs 70.8 ± 3.1 kg).

Discussion

These analyses confirm the efficacy of different calcium antagonists in the monotherapy of patients with mild to moderate essential hypertension.[1–4] All drugs used in this study proved to be equally efficacious in both group and intraindividual comparisons. However, the dihydropyridine derivatives nifedipine and nitrendipine caused somewhat more adverse effects than did verapamil. Our experience with diltiazem is small but a low incidence of adverse effects has been reported for this drug.[10] Verapamil and diltiazem, however, should be used with caution in patients with sinus or atrioventricular nodal dysfunction or severely impaired cardiac contractility. Thus, better tolerated calcium antagonists without adverse effects on the heart are still needed. In dihydropyridine-treated patients, the antihypertensive effect was sustained over a mean observation period of 3 months without evidence of volume retention or reflex tachycardia, while the decrease in heart rate in verapamil-treated patients was probably due to the drug's negative chronotropic effects. The constellation of unchanged heart rate and absence of volume retention may explain why calcium antagonists remain effective during long-term monotherapy of hypertension. The mechanisms behind these findings are not apparent from our study

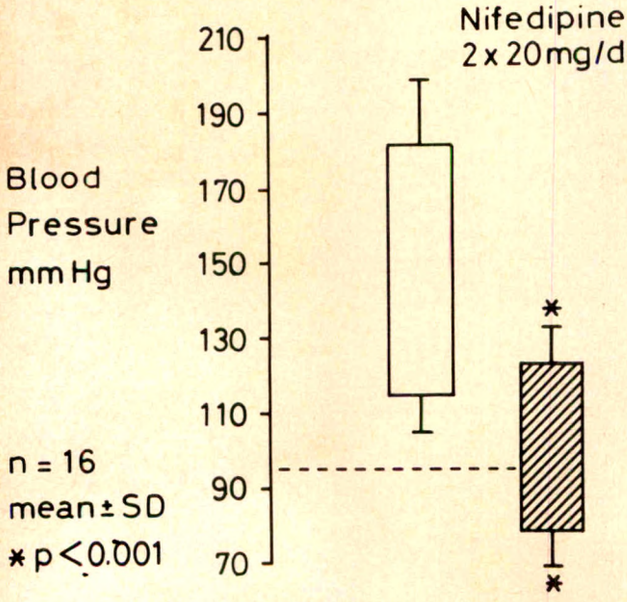

FIGURE 3. Response of blood pressure to nifedipine therapy in 16 black African essential hypertensive patients. SD = standard deviation.

but a diuretic effect,[11] interference with the renin-angiotensin-aldosterone system,[12] resetting of arterial baroreflexes[5] and interference with sympathetic mechanisms[13,14] must be considered.

Age, pretreatment blood pressure and plasma renin activity had significant and independent predictive effects with respect to the antihypertensive efficacy of calcium antagonists. However, none of the linear correlations at first seemed sufficiently close to be of help in guiding the clinical use of calcium antagonists in patients with hypertension. In particular, the correlation between pretreatment blood pressure and antihypertensive response is not unique to calcium antagonists; it applies to other antihypertensive drugs as well.[15]

Despite the weak linear relation between patient age and antihypertensive effect of calcium entry blockers, age nevertheless seems to be the most useful predictor of response to calcium antagonists. Thus, patients older than 60 almost uniformly showed a considerable decrease in blood pressure. Not only did older subjects show a greater average fall in blood pressure, but also a significantly greater proportion of them had normalized diastolic pressure compared with the other patients. We can only speculate about the reason for this good response. Reduced baroreflex sensitivity is known to occur with older age and hypertension.[16] Therefore, arterial vasodilatation and decrease in blood pressure might lead to less reflex stimulation, which could enhance the antihypertensive action of a calcium antagonist. Pharmacokinetic differences such as increased bioavailability in older patients could also play a role, but the potential importance of these factors remains to be defined.

It is also of interest in this context that patients with low renin activity and black patients seemed to respond particularly well to calcium antagonists. Black patients are known to have a high incidence of low renin hypertension[8] and this subset of patients is also characterized by poor counterregulatory mechanisms;[17] both of these findings could serve to explain our clinical observations. However, confirmatory experience is needed before calcium antagonists can be widely recommended in black patients.

It is also noteworthy that the incidence of adverse effects in older patients was similar to that in younger patients. Diuretics have often been used in older low renin patients[18] and in black patients,[19] but the widespread use of these drugs has been clouded by the suggestion of increased cardiovascular mortality, as well as other adverse effects, despite satisfactory blood pressure control.[20] Calcium antagonists might thus be an attractive alternative to diuretics for treatment of hypertension in older low renin patients and in black patients as well.

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Effects of Diltiazem on Serum Lipids, Exercise Performance and Blood Pressure: Randomized, Double-Blind, Placebo-Controlled Evaluation for Systemic Hypertension

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Treatment of hypertension with diuretics, β blockers and α blockers may be associated with adverse effects on exercise performance, serum lipids and blood chemistries, as well as with orthostatic effects and fluid retention. A randomized, double-blind, placebo-controlled trial of a sustained-release preparation of diltiazem as sole therapy for moderate essential hypertension was conducted. Diltiazem was administered 2 times a day (360 mg/day) to 16 patients and placebo to 14 patients in a 12-week study. Average supine blood pressure with diltiazem therapy fell from 161/100 to 144/87 mm Hg without fluid retention or orthostatic effects. In an open-label study, patients from the placebo and diltiazem groups continued with diltiazem therapy. At an average of over 8 months, supine blood pressure on diltiazem was 147/88 mm Hg, and after withdrawal to single-blind placebo, average supine blood pressure increased to 173/104 mm Hg. All changes were significant compared with baseline and placebo ($p < 0.01$). On diltiazem therapy, maximal treadmill exercise was increased by an average of 55 seconds ($p < 0.01$), whereas heart rate, blood pressure and double product (heart rate × blood pressure) were reduced at submaximal exercise, and heart rate and double product were reduced at maximal exercise. No changes in serum glucose, potassium or uric acid were found. No adverse effects on serum lipids occurred. Diltiazem treatment was associated with an increase in high-density lipoprotein cholesterol (52 to 60 mg/dl, $p < 0.006$) and a decrease in total cholesterol:high-density lipoprotein cholesterol ratio (4.7 to 4.2, $p < 0.05$). Adverse reactions to diltiazem were not severe, and only modestly greater than adverse reactions to placebo. Thus, diltiazem is an acceptable monotherapy in moderate essential hypertension with certain significant advantages over diuretics and β blockers.

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The antihypertensive effects of calcium-channel blockers have been well known for years,[1] but until recently, their therapeutic role has been considered secondary.[2] A growing realization of the potential adverse effects of the most common first-line agents—β blockers and diuretics[2]—and new knowledge of the role of calcium in hypertension[3] have led to the consideration of calcium-channel blockers as first-line therapy. As the stepped-care approach to hypertension is abandoned, the potential advantages of calcium-channel blockers over diuretics and β blockers should be considered.

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This study investigated, in a prospective, randomized, double-blind, placebo-controlled parallel trial, the effects of diltiazem as sole therapy in the treatment of moderate essential hypertension. Special attention was given to diltiazem's efficacy, both short and long term, its orthostatic effects and tolerability, its effects on blood chemistries, especially serum lipids, and its effects on exercise performance.

Methods

The protocol was approved by this institution's Human Research Committee, and each patient consented in writing to participate in the study.

Design: All patients entering the study were required to have essential hypertension—defined as a stable resting supine diastolic pressure between 95 and 110 mm Hg. All patients were withdrawn from any prior antihypertensive medication for at least 2 weeks and were placed on single-

blind placebo. After 7 to 10 days on placebo, the patients began a series of weekly visits, during which resting supine pressures were obtained; the average of 3 measurements was recorded as the pressure at each visit. For a subject to qualify, his or her resting supine diastolic pressure on 2 consecutive weekly visits had to be between 95 and 110 mm Hg and could not vary by more than 7 mm Hg between visits. The average of these 2 visits was used as baseline. Patients requiring more than 4 weeks for stabilization were considered labile and they were excluded. Patients were also excluded if they had other significant disease, sick sinus syndrome or greater than first-degree atrioventricular block. No patient was allowed to take any concomitant medication known to affect blood pressure, including oral contraceptives and psychotropics.

After baseline was established, each patient underwent dose titration with 1 capsule 2 times a day for the first 2 weeks, then 2 capsules 2 times a day for the second 2 weeks and 3 capsules 2 times a day for the third 2 weeks, if required. For those patients randomized to diltiazem, this made the daily dose 120, 240 and 360 mg, respectively, of the sustained-release preparation. Dosing continued upward until a 10% or greater reduction in diastolic pressure was achieved or until the highest dosage was reached. After a further 4-week administration period, a final evaluation was made (week 12). Electrocardiograms, routine hematologic studies, chemistry analysis and urinalysis were performed prestudy, at end of titration and at week 12.

After week 12, patients on diltiazem were allowed to continue on open-label diltiazem for an additional 10-month period, while those on placebo were allowed to begin titration and maintenance of open-label diltiazem. At the end of 10 months, a single-blind placebo withdrawal period was used to evaluate continuing blood pressure control. Patients on placebo were observed at 2-week intervals until supine diastolic blood pressure was >95 mm Hg, and 1 week after this they had another follow-up visit.

Measurements of blood pressure and heart rate: Patients were evaluated in the morning, 10 to 14 hours after their last dose of medication. They were asked to refrain from smoking or using caffeine-containing beverages before their visit and had been fasting for at least 2 hours. Measurements were made using the same arm and usually by the same person. Systolic and diastolic blood pressure were determined by phase I and V of the Korotkov sounds. Supine pressures were recorded after 10 minutes of rest with the arm positioned at the patient's side. Standing pressures were measured with the arm horizontal at the level of the fourth intercostal space at the sternum. Both supine and 5-minute standing pressures were based on an average of 3 determinations taken at least 1 minute apart. Pulses were counted for 30 seconds after the final pressure determination of a set. Immediate standing pressure was a single determination.

Exercise testing: Patients underwent exercise testing according to the Bruce protocol[4] at the prestudy visit (a "training" test), at the end of the placebo run-in (baseline), at the end of the titration period and at the end of the study (week 12). Blood pressure, heart rate, double product and ST change (V_5 and aVF) were obtained during the last 30 seconds of each 3-minute stage, at end of exercise and twice during recovery. Maximal exercise measurements were determined at the end of exercise.

Submaximal measurements were made at the end of the stage before the last stage of exercise during which more than 60 seconds of exercise occurred. If the patient failed to exercise 60 seconds into stage 2, the end of stage 1 was used as submaximal exercise.

Measurement of serum lipids: Serum lipid fractions were assessed by quantitating total cholesterol,[5] high-density lipoprotein (HDL) cholesterol,[6] low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, the total cholesterol:HDL cholesterol ratio and total triglycerides[7] at the prestudy visit (baseline), at end of titration and at end of week 12. Additional assessments were made at the end of long-term observation. All samples were drawn after a 14-hour fast.

Subjects: Fifty patients met the initial entry criteria and were enrolled in the placebo run-in after randomization (Table I). Thirteen of these (8 placebo and 5 diltiazem) failed to qualify during run-in, 1 patient in the diltiazem group requested withdrawal during this stage and 2 (1 in each group) were dropped for adverse reactions to placebo. Four patients (2 in each group) completed the entire trial and were found in retrospect not to have met stability criteria. They are treated in a separate analysis. The remaining 30 patients (14 placebo and 16 diltiazem) were analyzed in the parallel portion of the blood pressure data. These patients, plus the 4 just mentioned who completed the entire trial, constitute the patients in the analyses on exercise and adverse reactions. The same group, less 1 placebo patient who was excluded because of familial hyperlipidemia, constitutes the patients in the short-term lipid analysis. After the 12-week trial, 14 placebo patients began to take diltiazem, and they, together with 12 of the original diltiazem patients, are those analyzed in the long-term blood pressure trial. The long-term lipid analysis included the 33 patients from the short-term trial (with some of those on placebo beginning to take diltiazem) minus 2 placebo patients, 1 of whom never took diltiazem and another of whom had no lipid determination on diltiazem.

Statistical analysis: Demographic characteristics at baseline were compared using a χ^2 test for sex, race and smoking characteristics and Student's t test for age, weight and duration of hypertension to validate the randomization process.[8] To determine whether the diltiazem group and the placebo group were comparable at baseline, Student's t tests were performed for each key parameter using only the baseline data. No significant differences were found for any parameter, with the exception that the randomization produced a significantly higher systolic and diastolic blood pressure in the placebo group both at submaximal and maximal exercise.

To determine whether diltiazem and placebo groups differed significantly at other times during the study, split-plot analyses of variance were performed on the differences from baseline. If the treatment by evaluation interaction was not statistically significant (i.e., the 2 treatments were similar for the response from end of titration to end of the study), an overall statement about the treatment (diltiazem versus placebo) could be made. For any parameters exhibiting treatment by evaluation interaction, Student's t tests were performed on the differences from baseline at each evaluation.

To determine whether significant changes from baseline occurred at any evaluation for either treatment, 2-way analyses of variance were performed by treatment for each parameter in each position using the actual data. If the overall F test for the evaluation effect was significant at the 0.05 level, Duncan's multiple comparison procedure was used to determine which evaluations differed significantly from baseline.

The significance of diltiazem's long-term effects on blood pressure and lipid levels was determined by the paired t test, comparing the last observation with the baseline determination for blood pressure and the prestudy value for lipids.

Categorical analysis was performed by determining whether patients achieved the goal blood pressure reduction of 10% of baseline supine diastolic pressure. At each evaluation, a 1-tailed Fisher's exact test was performed to compare the percentage of diltiazem and placebo patients reaching goal.[8]

TABLE I Summary of Patient Demographics

	Diltiazem (16)	Placebo (14)
Sex	10 M, 6 F	10 M, 4 F
Age (year ± SE)	60 ± 2	61 ± 3
Race	15 white, 1 other	14 white
Height (in ± SE): M	69 ± 1	68 ± 1
F	64 ± 1	63 ± 1
Weight (lb ± SE): M	182 ± 9	187 ± 7
F	157 ± 8	134 ± 6
Smoker	1 (+), 15 (−)	1(+), 13 (−)
Hypertension duration (years)	16 ± 2	14 ± 3

SE = standard error.

TABLE III Average Blood Pressure and Heart Rate (± SE) in the Long-Term Study—Average 34.4 Weeks (26 Patients)

	Baseline	Last Observation	p
Systolic (mm Hg)			
Supine	164 ± 4	147 ± 3	<0.0001
Standing (5 min)	165 ± 4	145 ± 3	<0.0001
Diastolic (mm Hg):			
Supine	100 ± 2	88 ± 2	<0.0001
Standing (5 min)	102 ± 2	88 ± 2	<0.0001
Heart Rate (beats/min):			
Supine	67 ± 2	66 ± 2	NS
Standing (5 min)	74 ± 2	70 ± 2	=0.032

NS = not significant; SE = standard error.

TABLE II Average Blood Pressure and Heart Rate (± SE) in the Controlled 12-Week Study in 30 Patients (16 Diltiazem [D], 14 Placebo [P])

	Baseline		End of Titration		End of Week 12	
	D	P	D	P	D	P
Systolic (mm Hg):						
Supine	165 ± 2	167 ± 6	145 ± 4†	169 ± 6	144 ± 5†	171 ± 7
Standing (5 min)	164 ± 5	168 ± 6	143 ± 4*	166 ± 6	149 ± 5*	171 ± 6
Diastolic (mm Hg):						
Supine	100 ± 1	100 ± 1	86 ± 2†	99 ± 1	87 ± 2†	101 ± 3
Standing (5 min)	103 ± 1	102 ± 2	89 ± 2†	100 ± 3	88 ± 2†	102 ± 3
Heart rate (beats/min):						
Supine	64 ± 2	69 ± 3	62 ± 2	71 ± 3	62 ± 2	70 ± 3
Standing (5 min)	69 ± 3	77 ± 3	68 ± 2	76 ± 3	70 ± 2	75 ± 4

* p <0.01 diltiazem versus placebo.
† p <0.001 diltiazem versus placebo.
SE = standard error; all blood pressures on diltiazem are significantly different from baseline, p <0.01; no blood pressure on placebo is significantly different from baseline; no heart rate is significantly changed from baseline on diltiazem or placebo.

A final analysis was made to include the 4 patients who failed eligibility criteria but who received the drug through the double-blind portion of the protocol. The analysis yielded the same qualitative results.

Results

Demographics: The results of randomization of patients to diltiazem or placebo did not indicate any significant differences owing to sex, age, race, size, smoking history, concomitant diseases or duration of hypertension (Table I). Baseline blood pressure values (± 1 standard error) in the group randomized to placebo averaged 167 ± 6/100 ± 1 mm Hg supine, and 168 ± 6/102 ± 2 mm Hg after standing for 5 minutes. These values did not differ from values of subjects randomized to diltiazem, which averaged 165 ± 2/100 ± 1 mm Hg supine and 164 ± 5/103 ± 1 mm Hg standing.

Dosage: For each patient, dosage was titrated for best response. All patients reached a daily dosage of 360 mg of the sustained-release preparation of diltiazem, which was given 2 times a day.

Effects on blood pressure: Both systolic and diastolic blood pressure values were significantly reduced in patients treated with diltiazem compared with those receiving placebo. This was true for blood pressure taken in both the supine ($p < 0.001$) and the standing ($p < 0.01$) position at end of titration and at week 12 after 4 weeks of maintenance therapy at a constant dosage (Table II).

Average supine blood pressure at end of titration and at week 12 in the placebo group was 169/99 and 171/101 mm Hg, respectively. In those patients treated with diltiazem, average supine blood pressure was 145/86 at end of titration and 144/87 mm Hg at week 12. Average standing blood pressure at end of titration and at week 12 was, in the placebo group, 166/100 and 171/102 mm Hg, respectively, whereas in the group treated with diltiazem it was 143/89 and 149/88 mm Hg, respectively.

Supine diastolic pressure was reduced 10% or more in 11 of 16 patients treated with diltiazem compared with 1 of 14 patients treated with placebo ($p < 0.0007$) at end of titration. At week 12, 10 of 16 patients treated with diltiazem showed a 10% or more reduction of blood pressure, compared with 1 of 14 treated with placebo ($p = 0.002$).

Long-term effects of diltiazem on blood pressure were evaluated in 26 patients—those randomized to diltiazem who continued on treatment after the medium-term study and those who finished the medium-term study on placebo and were then placed on open-label diltiazem therapy. These subjects were followed for an average of 34.4 ± 11.4 (standard deviation) weeks (Table III). At their last observation, these patients had an average supine blood pressure of 147/88 mm Hg, compared with their baseline value of 164/100 mm Hg ($p < 0.0001$). In the standing position, the last observation blood pressure was 145/88 mm Hg, com-

TABLE IV Exercise Data in the Controlled 12-Week Study in Diltiazem (D)- and Placebo (P)-Treated Patients

		Submaximal Exercise		Maximal Exercise (end)		End of week 12 Versus Baseline	
		Baseline	End of Week 12	Baseline	End of Week 12	Submaximal	Maximal
Time (s)	D	—	—	602 ± 61	657 ± 58	—	<0.01
	P	—	—	674 ± 47	692 ± 44	—	NS
SBP (mm Hg)	D	193 ± 5	179 ± 6	201 ± 5	191 ± 5	<0.05	NS
	P	208 ± 6	218 ± 5	218 ± 6	220 ± 6	NS	NS
DBP (mm Hg)	D	99 ± 3	88 ± 3	88 ± 8	73 ± 7	<0.01	NS
	P	104 ± 2	103 ± 3	88 ± 7	77 ± 9	NS	NS
HR (beats/min)	D	137 ± 5	120 ± 5	158 ± 5	145 ± 5	<0.01	<0.01
	P	143 ± 3	139 ± 4	164 ± 3	164 ± 4	NS	NS
DP × 100	D	266 ± 13	222 ± 15	317 ± 12	279 ± 11	<0.01	<0.01
	P	297 ± 10	304 ± 12	358 ± 11	358 ± 9	NS	NS
ST V_5 (mm)	D	−0.3 ± 0.2	−0.2 ± 0.1	−0.6 ± 0.3	−0.2 ± 0.2	NS	NS
	P	−0.5 ± 0.3	−0.4 ± 0.3	−0.8 ± 0.3	−0.5 ± 0.3	NS	NS
ST aVF (mm)	D	−0.5 ± 0.2	−0.2 ± 0.2	−0.7 ± 0.3	−0.2 ± 0.2	<0.05	<0.01
	P	−0.6 ± 0.4	−0.3 ± 0.4	−0.8 ± 0.4	−0.5 ± 0.5	NS	NS

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; DP × 100 = double product (SBP × HR) × 100; ST V_5 = ST-segment position in V_5; ST aVF = ST-segment position in aVF; NS = not significant.

At maximal exercise, significant differences occurred between diltiazem and placebo in HR ($p = 0.0004$) and DP × 100 ($p = 0.0004$); at submaximal exercise, significant differences occurred between diltiazem and placebo in SBP ($p < 0.01$), DBP ($p < 0.03$), HR ($p < 0.0001$) and DP × 100 ($p < 0.0001$).

pared with a baseline value of 165/102 mm Hg ($p < 0.0001$).

To be certain that the amelioration in blood pressure observed long-term was not due to improvement in underlying disease, 12 patients were withdrawn to single-blind placebo after 10 months of open diltiazem administration. They were seen every 2 weeks until supine diastolic blood pressure was >95 mm Hg, and then observed again 1 week later. This blood pressure level was reached in 2 weeks by 7 patients, in 3 weeks by 1 (who was on vacation at 2 weeks), in 4 weeks by 2 and in 6 weeks by 1. Average baseline supine pressure in this group was 173/104 mm Hg; at last diltiazem observation, it was 144/84 mm Hg; at an average of 2.6 weeks after withdrawal, it was 172/100 mm Hg; and 1 week later, it was 170/100. Standing pressure values followed a similar pattern.

Effects on heart rate: No clinically significant changes in heart rate were produced by treatment with either placebo or diltiazem. A small, statistically significant ($p = 0.032$) decrease in heart rate was noted during the long-term study, in the standing position only, where the heart rate fell from an average of 74 to 70 beats/min (Tables II and III).

Orthostatic effects: Orthostatic effects on heart rate and blood pressure in patients treated with diltiazem were compared with those in patients treated with placebo at the end of 12 weeks. A small and essentially identical drop in systolic pressure was noted in each group, with no change in diastolic pressure. In the placebo group, supine pressure fell from 171/101 to 167/102 mm Hg immediately upon standing, whereas with diltiazem patients, the pressure fell from 144/87 to 142/87 mm Hg. The reflex increase in heart rate was similar in both groups.

Effects on exercise performance (Table IV): In the 12-week study, the maximum duration of exercise increased an average of 55 seconds in the diltiazem group ($p < 0.01$) and 18 seconds in the placebo group (difference not significant) compared with baseline.

TABLE V Average Serum Lipid Levels (± SE) in the Controlled 12-Week Study (33 Patients, 18 Diltiazem [D], 15 Placebo [P])

		Baseline	End of Week 12	p
Cholesterol (mg/dl)	P	222 ± 10	225 ± 9	NS
	D	231 ± 7	245 ± 8	NS
HDL (mg/dl)	P	52 ± 6	54 ± 4	NS
	D	49 ± 3	56 ± 4	<0.05
LDL (mg/dl)	P	145 ± 9	146 ± 8	NS
	D	159 ± 7	164 ± 6	NS
VLDL (mg/dl)	P	25 ± 3	24 ± 3	NS
	D	25 ± 3	25 ± 3	NS
Cholesterol/HDL	P	4.74 ± 0.39	4.43 ± 0.33	NS
	D	4.99 ± 0.28	4.62 ± 0.33	NS
Triglycerides	P	126 ± 16	118 ± 18	NS
	D	127 ± 15	120 ± 13	NS

HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; NS = not significant; SE = standard error.

No significant differences between diltiazem and placebo were found.

However, the difference between the groups was not significant. Blood pressure, heart rate and double product (heart rate × blood pressure) were all significantly decreased by diltiazem at submaximal exercise, whereas only heart rate and double product were decreased at maximal exercise. The differences from baseline values at maximal exercise were smaller than those at submaximal exercise. These same parameters, which were significantly different from baseline, were also significantly different from placebo (see Table IV). There was significantly less ST-segment depression in lead aVF in the diltiazem group at end of week 12 compared with baseline, both at submaximal and maximal exercise, but this difference was not significant compared with placebo, and its clinical significance is uncertain.

Effects on serum lipids and blood chemistries: In the medium-term 12-week study (Table V), the only significant change in serum lipids was an increase in HDL cholesterol in the diltiazem group from 49 ± 3

TABLE VI Average Serum Lipids (± SE) in the Long-Term Study—Average 29.5 Weeks (31 Patients)

	Baseline	Last Observation	p
Chloesterol (mg/dl)	227 ± 6	233 ± 7	NS
HDL (mg/dl)	52 ± 3	60 ± 3	<0.006
LDL (mg/dl)	150 ± 5	148 ± 7	NS
VLDL (mg/dl)	24 ± 2	25 ± 2	NS
Cholesterol/HDL	4.7 ± 0.2	4.2 ± 0.2	<0.05
Triglycerides (mg/dl)	120 ± 12	126 ± 11	NS

Abbreviations as in Table V.

TABLE VII Adverse Reactions During Controlled 12-Week Study (34 Patients, 18 Diltiazem [D], 16 Placebo [P])

	D	P
Dizziness	3	1
Edema	3	0
Asthenia	2	2
Constipation	2	0
Dyspnea	2	0
Dyspepsia	2	0
Nocturia	2	1
Paresthesia	1	2
Headache	1	4
Nausea	0	2
Insomnia	0	2
Chest pain	0	2
Other	5	6
Total	23	22

All adverse effects that occurred more than once in either the diltiazem or placebo group are listed, regardless of severity. Those occurring only once are listed under "other."

to 56 ± 4 mg/dl ($p < 0.05$) between baseline and week 12. Other changes that exceeded 5% in magnitude but that were not statistically significant were an increase in cholesterol from 231 to 245 mg/dl in the diltiazem group and a fall in cholesterol:HDL ratio and triglycerides in both groups.

In the long-term study, which involved 31 patients for an average of 29.5 weeks, HDL cholesterol increased from 52 ± 3 to 60 ± 3 mg/dl ($p < 0.006$), and the cholesterol:HDL ratio decreased from 4.7 ± 0.2 to 4.2 ± 0.2 ($p < 0.05$). No other changes greater than 5% in magnitude occurred (Table VI). No clinically or statistically significant changes were found in any analysis of serum glucose, creatinine, potassium or uric acid.

Adverse reactions: Thirty-four patients completed the medium-term 12-week study. Nine of the 16 placebo patients reported a total of 22 adverse reactions; 12 of the 18 diltiazem patients reported a total of 23 adverse reactions (Table VII). Only headache in the placebo group, and dizziness and edema in the diltiazem group, were reported by more than 2 patients. Minor abnormalities in the laboratory values occurred equally in the diltiazem and placebo groups.

Discussion

We investigated the benefits of diltiazem as sole therapy in moderate essential hypertension. Diuretics, β blockers and, to a lesser extent, α blockers have been used as initial therapy in hypertension in spite of significant adverse effects. Diuretics cause impotence, hypokalemia and adverse effects on serum lipids[9] and blood chemistries, as well as possible increased mortality in some groups.[10] Beta blockers impair exercise performance[11,12] and some have adverse lipid effects.[13,14] Paradoxical pressor responses[15] and a fairly high incidence of lack of response are also a problem in using β blockers, as are a number of diseases that contraindicate their use. The α blockers are limited in use because fluid retention, tachycardia and significant orthostatic effects may occur, as well as tachyphylaxis when used as sole therapy.

As shown in the present study, diltiazem does not share these adverse effects, in spite of the fact that upward dose titration was vigorous—up to a daily dosage of 360 mg in all patients. The strict criteria for blood pressure stability in this study were reflected in the lack of placebo response both in terms of mean pressure change and attainment of goal response. In contrast, the diltiazem-treated patients showed a very acceptable response to treatment, with a decrease in average supine blood pressure from 165/100 to 144/87 mm Hg over 12 weeks. At more than an average of 8 months of treatment, average pressure remained at 147/88 mm Hg, but when patients were withdrawn to single-blind placebo, average supine blood pressure rose from 144/84 to 170/100 mm Hg.

Several studies[16–20] of exercise tolerance in hypertensive patients who were treated with various agents (diuretics, methyldopa and β blockers) until normotension was achieved found no significant decrease in exercise tolerance after treatment. Invasive studies,[16,19] however, show that patients receiving β blockers must compensate for decreased inotropy and chronotropy with an increase in stroke volume and arterial-mixed venous oxygen difference, an ability that decreases with age. Bruce et al[16] also showed that the exercise response to treatment was related to the underlying integrity of the recipient's circulatory system.

The studies just mentioned were conducted in patients who were an average of 15 to 20 years younger than those in the present study. The diltiazem-treated group in our study significantly increased maximal exercise duration by 55 seconds ($p < 0.01$), whereas the placebo group exercised an average of 18 seconds more than at baseline (difference not significant). The blunting in heart rate and pressor response to exercise in the diltiazem-treated patients was greater at submaximal than at maximal exercise. The fact that these patients could significantly increase their exercise performance at a mean age >60 years indicates that inotropy was not depressed and that normalized peripheral resistance allowed a ready increase in the stroke volume. Thus, diltiazem appears to normalize the response to exercise (at least with regard to blood pressure) rather than impair it, and may tend to increase exercise tolerance in hypertensive patients as it does in those with angina.[21]

There were no adverse effects on serum glucose, potassium or uric acid levels such as those seen with diuretic administration.

When patients are enrolled in any study of cardiovascular disease, there are often subtle behavioral changes with regard to diet, exercise and other habits, which are difficult to control. However, it does appear that the use of diltiazem is associated with a significant increase in HDL cholesterol in this population. Whether this change is clinically beneficial remains to be seen. It is clear that the adverse lipid effects seen with diuretics and β blockers are not seen with diltiazem. This may reflect a mechanism similar to that responsible for the potentially positive lipid effects of prazosin.[22,23]

Serious adverse reactions to diltiazem were not seen. In consonance with prior experience in the use of diltiazem for the treatment of angina,[24] adverse reactions to diltiazem were quantitatively not very different from those to placebo. Reactions that have been recognized as possibly associated with diltiazem, such as dizziness, edema, constipation and dyspepsia, were neither common nor severe.

When compared with standard therapies for hypertension, such as diuretics and β blockers, diltiazem's major disadvantages are cost and the 2-times-a-day dosage regimen. There are, however, several major advantages: diltiazem shows both short- and long-term effectiveness and is well tolerated; it does not impair exercise performance; it has no adverse effects on blood chemistries; it does not have an adverse effect, and may even have a positive effect, on serum lipids; and it does not cause orthostatic effects, fluid retention or tachycardia. Thus, it can be concluded that diltiazem is an acceptable monotherapy in patients with moderate essential hypertension.

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Diuretics Versus Calcium-Channel Blockers in Systemic Hypertension: A Preliminary Multicenter Experience with Hydrochlorothiazide and Sustained-Release Diltiazem

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The safety and efficacy of sustained-release diltiazem 120 to 180 mg, 2 times a day, were compared with hydrochlorothiazide 25 to 50 mg, 2 times a day, and the combination of diltiazem and hydrochlorothiazide in 56 patients with mild to moderate hypertension (supine diastolic blood pressure between 95 and 114 mm Hg) using a placebo-controlled, parallel-design protocol. Data from an additional 21 patients were evaluated for safety only. The data reported herein represent the preliminary experience from a larger 200-patient multicenter study. All patients received placebo for 4 weeks, followed by either hydrochlorothiazide or diltiazem titrated to achieve a diastolic blood pressure reduction of ≥10 mm Hg to reach a goal supine diastolic blood pressure of <90 mm Hg. Patients not achieving the treatment goal received hydrochlorothiazide plus diltiazem.

At week 14, on maintenance monotherapy, diltiazem and hydrochlorothiazide produced comparable reductions in blood pressure from placebo baseline (160.3 ± 24.3/101.7 ± 5.5 to 145.2 ± 24.1/89.8 ± 7.4 mm Hg with diltiazem, 156.0 ± 15.6/103.7 ± 4.7 to 134.1 ± 12.5/89.2 ± 9.5 mm Hg with hydrochlorothiazide, p <0.001 for both). Diltiazem and hydrochlorothiazide achieved goal blood pressure in 42% and 45% of patients, respectively. The effects in responders were sustained for 6 months. In patients who did not achieve the treatment goal, 63% responded to diltiazem plus hydrochlorothiazide. No clinically significant postural hypotension was observed on any regimen. Heart rate was slightly lower with diltiazem than with hydrochlorothiazide. Adverse effects were minimal with diltiazem, hydrochlorothiazide and diltiazem plus hydrochlorothiazide but more hypokalemia occurred with hydrochlorothiazide.

Sustained-release diltiazem used twice daily provided safe and effective therapy for mild to moderate hypertension when used alone or in combination with hydrochlorothiazide. As a monotherapy, sustained-release diltiazem is similar in efficacy to hydrochlorothiazide.

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Calcium-channel blockers are a distinct group of compounds that interfere with the normal transmembrane flux of extracellular calcium, on which vascular tissue depends for contraction and impulse generation.[1] They reduce the contractile activity of the myocardium and promote coronary and systemic arterial dilation.[1] These hemodynamic effects provide the clinical rationale for the use of calcium-channel blockers in the management of ischemic heart disease[1] and hypertrophic cardiomyopathy.[2]

Because systemic arterial dilation can be expected to reduce elevated arterial blood pressure, there has been considerable enthusiasm for the use of calcium-channel blockers in the medical management of sys-

temic hypertension and hypertensive emergencies.[3–8] The effectiveness and safety of these drugs in the treatment of systemic hypertension have been clearly documented.[3–6,8–13] The efficacy of nifedipine and verapamil appears comparable to that of oral diuretics in hypertension.[3,8,9,14,15] In this report, we describe a preliminary experience from a large multicenter trial designed to be the first well-controlled study comparing sustained-release diltiazem with hydrochlorothiazide in patients with systemic hypertension.

Methods

The data presented are based on a preliminary analysis of 77 patients who are part of a 200-patient multicenter study still in progress.

Patient selection: A total of 77 patients with mild to moderate systemic hypertension were enrolled after written and informed consent was obtained. Fifty-six patients were analyzed for safety and efficacy; 21 for safety only. The demographics of the 56-patient study group are listed in Table I.

All patients who were entered had essential hypertension with a stable resting supine diastolic pressure between 95 and 114 mm Hg while not taking medication. Potential patients were seen before the study, and were entered into a placebo run-in screening phase after all previously administered antihypertensive medication had been stopped for at least 2 weeks. For entry, stable resting supine diastolic pressures (each recorded pressure was the averge of 3 readings using Korotkov phase V) between 95 and 114 mm Hg and varying by $< \pm 7$ mm Hg were required on 2 consecutive weekly visits starting with days 7 to 10 of the placebo run-in screening. If a patient needed more than 4 weeks to stabilize, he or she was considered labile and excluded from further study participation.

Patients with the following conditions were excluded from the study: significant cardiovascular disease other than essential hypertension, impaired renal function, greater than first-degree heart block, sick sinus syndrome, known abuse of alcohol or drugs, pregnancy and known hypersensitivity to thiazides or other sulfonamide-derived drugs.

Experimental design: The design of the multicenter trial is shown in Figure 1. A single-blind, placebo run-in screening of at least 2 weeks was used to establish baseline pressures. Eligible patients were then randomized to treatment with hydrochlorothiazide or sustained-release diltiazem in a double-blind, parallel fashion, using the double-dummy technique. A titration period of up to 2 months then commenced;

TABLE I Demographic Summary

	Diltiazem (n = 26)	Hydrochlorothiazide (n = 30)
Sex		
Men	15	21
Women	11	9
Age (years)	55 ± 10	56 ± 10
Race		
Black	12	14
Other	14	16
Height (inches)		
Men	70 ± 3	69 ± 2
Women	64 ± 4	64 ± 2
Weight (pounds)		
Men	221 ± 50	196 ± 29
Women	167 ± 33	160 ± 29
Smokers		
Yes	4	7
No	22	23
Duration of hypertension (years)	11 ± 8	11 ± 8

patients were given increasing doses of study medications (240 to 360 mg/day diltiazem; 50 to 100 mg/day hydrochlorothiazide, each in 2 divided doses) until optimal response was reached. Optimal response was either a reduction in supine diastolic blood pressure to <90 mm Hg or a reduction of at least 10 mm Hg for those patients with baseline pressures of 95 to 99 mm Hg. Upon achievement of the optimal response, patients entered an evaluation period for 4 weeks. Patients who achieved and maintained goal pressure reduction with the initial medication remained on that medication and were seen monthly for 3 months.

After the evaluation period, any patient who had not achieved and maintained the goal diastolic blood pressure received the other medication in unblinded fashion (titrated to optimum over a 2-month period) in addition to the initial medication. Upon reaching the optimal dose of the second medication, patients were followed for an additional 1 to 2 months to assess the safety and effectiveness of the combination therapy.

Methods of observation: Resting supine, immediate and 5-minute standing blood pressures were measured 10 to 12 hours after the last dose of medication and before the next dose. Safety was monitored during the placebo and active treatment phases with adverse-effect profiling, electrocardiograms, complete blood counts and blood chemistries.

Statistical analysis: The experiment was designed with stratification by investigator to detect and adjust for any investigator differences in the treatment comparisons. However, because of the imbalance of patient and treatment

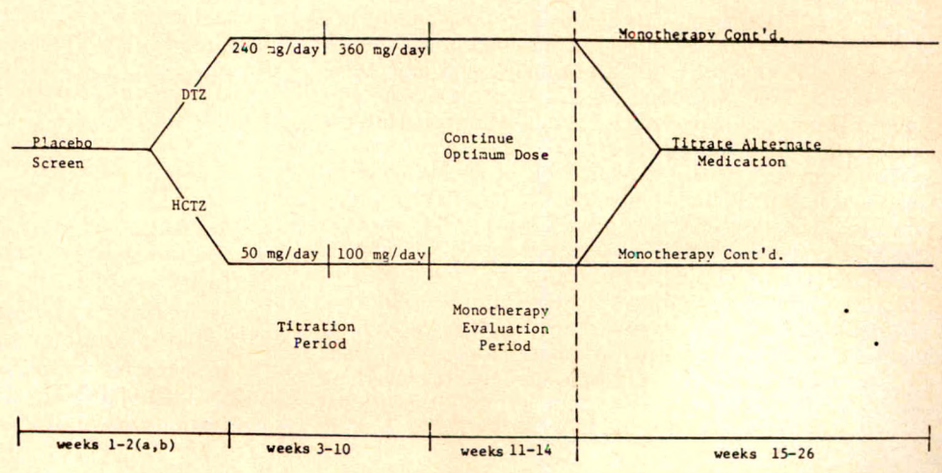

FIGURE 1. Study design for a multicenter comparison of hydrochlorothiazide (HCTZ) and sustained-release diltiazem (DTZ).

TABLE II Mean (± Standard Deviation) Supine Blood Pressure and Heart Rate on Monotherapy (All Patients) (p Values Versus Baseline)

	Baseline		End of Monotherapy Titration (Week 10)		Week 14	
	Diltiazem (n = 26)	HCTZ (n = 29)	Diltiazem (n = 26)	HCTZ (n = 29)	Diltiazem (n = 26)	HCTZ (n = 29)
SBP (mm Hg)*	160 ± 24	156 ± 16	145 ± 23 p = 0.0001	136 ± 13 p = 0.0001	145 ± 24 p = 0.0008	134 ± 13 p = 0.0001
DBP (mm Hg)*	102 ± 6	104 ± 5	89 ± 7 p = 0.0001	91 ± 7 p = 0.0001	90 ± 7 p = 0.0001	89 ± 10 p = 0.0001
MAP (mm Hg)*	121 ± 11	121 ± 8	107 ± 11 p = 0.0001	106 ± 8 p = 0.0001	108 ± 12 p = 0.0001	104 ± 10 p = 0.0001
HR (beats/min)*	76 ± 9	73 ± 7	71 ± 9 p = 0.0069	72 ±10 NS	69 ± 10 p = 0.0088	71 ±10 NS

DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; HR = heart rate; MAP = mean arterial pressure; NS = not significant; SBP = systolic blood pressure.

TABLE III Mean (± Standard Deviation) Changes in Supine Blood Pressure and Heart Rate from Baseline on Monotherapy (All Patients) (p Values Versus Therapies)

	End Monotherapy Titration (Week 10) − Baseline		Week 14 − Baseline		
	Diltiazem (n = 26)	HCTZ (n = 29)	Diltiazem (n = 26)	HCTZ (n = 29)	Overall *p* Value*
SBP (mm Hg)	−15 ± 14	−21 ± 17	−15 ± 20	−22 ± 18	NS
DBP (mm Hg)	−13 ± 7	−13 ± 7	−12 ± 8	−14 ± 11	NS
MAP (mm Hg)	−14 ± 8	−16 ± 10	−13 ± 11	−17 ± 12	NS
HR (beats/min)	−5 ± 8	−0.3 ± 9	−7 ± 12	−1 ± 7	0.0348

Abbreviations as in Table II.
* Overall differences between diltiazem and HCTZ therapies.

groups among the various participating medical centers resulting from the interim data, we have simply pooled the sites for this analysis. We have avoided comparison of groups that achieved goal diastolic blood pressure on monotherapy with groups that did not achieve goal on combined therapy because of possible confusion in interpretation due to the different selection processes of these groups.

Baseline comparisons were made to test for differences in the treatment groups. For the parameters of sex, race, age, classification and smoking status, Fisher's exact test for 2 × 2 tables was used. For the parameters of duration of hypertension, diastolic blood pressure, systolic blood pressure, mean arterial pressure and heart rate, a *t* test for independent samples was used.

Fisher's exact test for independence using 2 × 2 tables was used to analyze diastolic blood pressure goal achievement by comparing (1) diltiazem with hydrochlorothiazide at week 14, (2) diltiazem blood pressure-goal achievers on monotherapy with hydrochlorothiazide-goal achievers on monotherapy at week 26 and (3) diltiazem-non-goal achievers on combined therapy with hydrochlorothiazide-non-goal achievers on combined therapy at week 26.

The *t* tests were then used to analyze the mean change by treatment in supine, immediate and 5-minute standing systolic and diastolic blood pressures, mean arterial pressure and heart rate. Analysis-of-variance methods, accounting for between- and within-patient variability, were used to compare (1) diltiazem with hydrochlorothiazide up to week 14, (2) diltiazem-goal achievers on monotherapy with hydrochlorothiazide-goal achievers on monotherapy over weeks 14, 18, 22 and 26 and (3) diltiazem-non-goal achievers on combined therapy with hydrochlorothiazide-non-goal achievers on combined therapy over weeks 14, 22 and 26. Comparisons between hydrochlorothiazide and diltiazem were made dependent on a check for treatment-by-evaluation interaction. If the interaction was significant, comparisons were made and reported at each evaluation. If the interaction was not significant, an overall treatment main-effect comparison, which averages over evaluations, was reported. In addition, a covariance analysis on the week 14 data was used to check for response differences because of other identifiable factors, including age and race.

To evaluate the potential for postural hypotension, differences between immediate standing and resting supine systolic and diastolic blood pressures, mean arterial pressure and heart rate were examined. Analysis-of-variance tests of these differences were used to compare (1) diltiazem with hydrochlorothiazide over baseline and week 14, (2) diltiazem-goal achievers on monotherapy with hydrochlorothiazide-goal achievers on monotherapy over weeks 14 and 26 and (3) diltiazem-non-goal achievers on combined therapy over weeks 14 and 26. These evaluations were made for each group in total, as well as for subsets of each group based on age.

Results

A total of 77 patients were enrolled; 56 could be evaluated for both safety and efficacy. The other 21 patients could not be analyzed for the following reasons: inability to tolerate medications (7); noncompliance with dosing instructions (7); and withdrawals for other reasons, including protocol violations and other illness (7). The data from these patients are included in the safety analysis.

TABLE IV Mean (± Standard Deviation) Immediate Standing Blood Pressure and Heart Rate on Monotherapy (All Patients) (p Values Versus Baseline)

	Baseline		End of Monotherapy Titration (Week 10)		Week 14	
	Diltiazem (n = 26)	HCTZ (n = 30)	Diltiazem (n = 26)	HCTZ (n = 30)	Diltiazem (n = 26)	HCTZ (n = 30)
SBP (mm Hg)*	159 ± 25	150 ± 12	141 ± 15 p = 0.0001	129 ± 17 p = 0.0001	138 ± 23 p = 0.0008	127 ±18 p = 0.0001
DBP (mm Hg)*	102 ± 7	104 ± 7	88 ± 9 p = 0.0001	90 ± 13 p = 0.0001	86 ± 8 p = 0.0001	90 ± 14 p = 0.0001
MAP (mm Hg)*	121 ± 13	119 ± 7	106 ± 8 p = 0.0001	103 ± 13 p = 0.0001	103 ± 11 p = 0.0001	102 ± 14 p = 0.0001
HR (beats/min)*	81 ± 9	78 ± 8	78 ± 10 NS	82 ± 8 p = 0.0152	76 ± 13 p = 0.0208	76 ± 12 NS

Abbreviations as in Table II.
* No statistical intergroup differences at baseline

TABLE V Mean (± Standard Deviation) 5-Minute Standing Blood Pressure and Heart Rate on Monotherapy (All Patients) (p Values Versus Baseline)

	Baseline		End of Monotherapy Titration (Week 10)		Week 14	
	Diltiazem (n = 26)	HCTZ (n = 29)	Diltiazem (n = 26)	HCTZ (n = 29)	Diltiazem (n = 26)	HCTZ (n = 29)
SBP (mm Hg)*	157 ± 23	157 ± 18	141 ± 19 p = 0.0001	136 ± 15 p = 0.0001	142 ± 19 p = 0.0001	131 ±16 p = 0.0001
DBP (mm Hg)*	104 ± 8	106 ± 8	92 ± 8 p = 0.0001	94 ± 9 p = 0.0001	88 ± 9 p = 0.0001	91 ± 12 p = 0.0001
MAP (mm Hg)*	122 ± 12	123 ± 10	108 ± 10 p = 0.0001	108 ± 10 p = 0.0001	106 ± 10 p = 0.0001	104 ± 12 p = 0.0001
HR (beats/min)*	83 ± 9	78 ± 9	77 ± 9 p = 0.0008	81 ± 7 NS	75 ± 10 p = 0.0016	79 ± 11 NS

Abbreviations as in Table II.
* No statistical intergroup differences at baseline

Blood pressure and heart rate: Both diltiazem and hydrochlorothiazide caused a significant reduction in systolic and diastolic blood pressures at week 10 (end of titration) and at week 14 (end of maintenance). The data for supine, immediate and 5-minute standing systolic, diastolic and mean blood pressures and heart rate are shown in Tables II through V. At week 14, the mean daily dose of diltiazem was 326 mg; for hydrochlorothiazide it was 79 mg.

The ability of diltiazem and hydrochlorothiazide to produce the goal reduction in supine and diastolic blood pressure was compared at week 14. Diltiazem produced the goal in 42% and hydrochlorothiazide in 45% of patients. In the patients maintained on diltiazem and hydrochlorothiazide monotherapy beyond week 14, the effects of therapy on blood pressure were maintained (observed at weeks 18, 22 and 26). At week 26, 91% of patients on diltiazem who achieved goal blood pressure at week 14 had maintained the goal pressure, while 73% of patients on hydrochlorothiazide maintained the goal blood pressure reduction.

The addition of hydrochlorothiazide to patients receiving diltiazem who did not achieve the goal pressure reduction at week 14 produced the goal pressure reduction in 6 of 11 patients (55%) at week 26. The addition of diltiazem to patients receiving hydrochlorothiazide who did not achieve the goal blood pressure at week 14 produced the goal pressure reduction in 10 of 14 patients who completed the study (71%).

Safety: Significant postural drops in blood pressures were not seen with either diltiazem or hydrochlorothiazide treatment. Significant adverse effects were minimal for diltiazem, hydrochlorothiazide and the combination. Four patients on diltiazem, 5 on hydrochlorothiazide and none on the combination discontinued participation because of adverse effects. No significant electrocardiographic abnormalities were noted. No significant alterations in laboratory values, other than those alterations in electrolytes consistent with thiazide therapy, were seen. Specifically, 7 patients became hypokalemic and 4 patients developed hyperuricemia on hydrochlorothiazide alone. On combination diltiazem and hydrochlorothiazide, the pattern was similar to that of hydrochlorothiazide alone: 8 patients developed hypokalemia and 7 patients developed hyperuricemia.

Discussion

Many of the calcium-channel blockers have been shown to be safe and effective for the treatment of systemic hypertension and hypertensive emergencies.[3–6,8–13,16,17] In this preliminary report of a large study of 200 patients, sustained-release diltiazem used twice daily was shown to be as effective as hydrochlo-

TABLE VI Hemodynamic and Metabolic Comparison of Diltiazem and Hydrochlorothiazide (HCTZ)

	Initial		Chronic	
	HCTZ	Diltiazem	HCTZ	Diltiazem
Vascular Volume	↓	←→	←→	←→
Total peripheral vascular resistance	↓	↓↓	↓↓	↓↓
Heart rate	←→	↓	←→	↓
Cardiac output	↓	←→	←→	←→
Blood pressure	↓	↓	↓	↓
Plasma renin activity	↑	↑←→	↑	↑←→
Natriuresis	↓↓	↓	↓↓	↓
Potassium	↓	←→	↓	←→
Lipids	↑	←→	↑	←→
Uric acid	↑	←→	↑	←→
Blood sugar (type II diabetics)	↑	←→	↑	←→

↑ = increase; ←→ = no net change; ↓ = decrease.

rothiazide used twice daily in reducing supine and standing blood pressure, both short and long term, in patients with mild to moderate systemic hypertension. Diltiazem was shown to cause a small but clinically insignificant reduction in heart rate compared with hydrochlorothiazide; whereas in the doses used, hydrochlorothiazide caused more hypokalemia. Both drugs were well tolerated.

Although diltiazem and hydrochlorothiazide are equally effective in the treatment of hypertension, they have different hemodynamic and metabolic effects (Table VI).[16,18–20] Diltiazem reduces blood pressure predominantly through its vasodilator actions, without causing tachycardia.[3,9] Calcium entry blockers have also been shown to have natriuretic effects.[16] They do not affect blood sugar, uric acid, lipids or potassium levels. Diuretics, such as hydrochlorothiazide, work initially by reducing intravascular volume and cardiac output; later, with physiologic adaptations to therapy, vascular volume returns to baseline, vascular resistance is reduced and cardiac output is maintained. Diuretics raise plasma renin activity and, unlike diltiazem, can cause hyperglycemia in type II diabetic patients, raise plasma lipids and uric acid and reduce serum potassium.[21,22]

With long-acting, sustained-release preparations now available, diltiazem and some other calcium-channel blockers can be considered first-line therapy and alternative therapy to β blockers and diuretics because of their favorable hemodynamic and metabolic characteristics and low adverse-effect profiles. They may become the treatment of choice in patients with hypertension and angina pectoris, for which they have proven efficacy.[23,24] Among the calcium-channel blockers, diltiazem has one of the lowest adverse effect frequencies[5] and should play an important role in the treatment of hypertension in years to come.

Implications: These preliminary findings confirm that sustained-release diltiazem is an effective agent in systemic hypertension with an antihypertensive potency similar to that of diuretics. Diltiazem has similar antihypertensive effects on other calcium-channel blockers. Because of the minimal adverse effects usually encountered with diltiazem and its intrinsic negative chronotropic action, it is likely to be useful as a single-drug treatment for hypertension. However, the higher cost of diltiazem and other calcium-channel blockers, compared with diuretic agents, may limit their use to patients in whom advantages in efficacy, adverse effect-profiles or compliance are shown.

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Antihypertensive Therapy with Calcium-Channel Blockers: Comparison with Beta Blockers

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As a result of concern about the safety and long-term toxicity of diuretics, there is a growing trend toward the use of alternative agents as initial therapy in essential hypertension. Worldwide, β blockers and vasodilators, especially the calcium-channel blockers, are the most commonly used alternative agents. Several studies comparing these 2 classes of medications are reviewed. These studies indicate that verapamil, nifedipine and diltiazem are all comparable in efficacy to β blockers. When combined, calcium-channel blockers and β blockers produce additive responses. These agents may differ in the relation between the magnitude of their antihypertensive effect and patients' pretreatment plasma renin activity and age. Younger persons and those with high plasma renin activity tend to respond better to β blockers; older subjects and those with low plasma renin activity are more consistently responsive to calcium-channel blockers. The choice of agent should be individualized, based upon accompanying illnesses, adverse-effect profile and demographic factors.

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Although the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure continues to recommend diuretics as the initial therapy in essential hypertension,[1] there is a growing trend toward the use of alternative agents. The main impetus for this shift has been increasing concern about the safety and long-term toxicity of diuretics. The electrolyte and metabolic derangements induced by diuretics have been recognized for many years. The suggestion, albeit poorly substantiated, from the Multiple Risk Factor Intervention Trial that diuretic therapy may be associated with an excessive incidence of sudden death[2] and the difficulty of demonstrating a decrease in coronary mortality despite successful antihypertensive therapy in several large trials using diuretics have accentuated these doubts.

A second reason for modifying the stepped-care approach is that patients with mild or moderate hypertension who are not controlled by diuretics alone may be controlled by other agents and, therefore, alternative drugs should be evaluated before resorting to combination therapy.[3] A third factor to consider is individualization of therapy in patients with multisystemic disease. Accordingly, a β blocker might be used in patients with hypertension and angina and prazosin might be tried in competitive athletes, while diuretics would be avoided in patients with gout or diabetes. Finally, the reduction in mortality and, in some instances, reinfarction by β blockers in secondary prevention trials[4,5] has encouraged many physicians to use these agents in hypertension with the hope that they are similarly effective in primary prevention, although evidence for this is lacking.

In the United States, β blockers are the most popular alternative to diuretics, and their use as initial therapy has been sanctioned by the Joint National Committee.[1] In Europe, the calcium-channel blockers are widely used as initial antihypertensive therapy. These agents have not yet been approved in the U.S. for this indication by the Food and Drug Administration, but marketing surveys suggest they are used widely in hypertension, nonetheless. This article will review studies in which these 2 classes of medications have been compared or used in combination therapy and it will attempt to place their use into a broader perspective.

Verapamil

Verapamil was the first calcium-channel blocker used in hypertension, and several trials comparing verapamil with β blockers have been published. Leonetti et al[6] evaluated 31 patients with mild to moderate hypertension who were withdrawn from previous therapy, and randomized to either propranolol, 60 to 80

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mg, 3 times a day, or verapamil, 120 to 180 mg, 3 times a day, for 6 weeks. Then, after a 3-week washout period, patients were crossed over to the alternative drug. Verapamil produced a somewhat greater reduction in both systolic and diastolic pressures than propranolol (31/20 vs 17/17 mm Hg), but this difference was not statistically significant. Heart rate fell significantly (by 14 beats/min) on propranolol, but not on verapamil (insignificant decrease of 3 beats/min). Hornung et al[7] evaluated the same 2 agents with interarterial pressure monitoring. Eighteen subjects completed an open-label, randomized crossover study in which propranolol and verapamil were titrated from 40 to 240 mg, 2 times a day, and 120 to 240 mg, 2 times a day, respectively, over 2 to 3 months. Both drugs produced similar antihypertensive responses, which were present at rest and during exercise. In addition, no differences in the 24-hour blood pressure profiles were noted. The frequency and severity of adverse effects were similar, with constipation predominating on verapamil and fatigue on propranolol.

Doyle[8] reported 2 studies—one comparing verapamil with pindolol in patients maintained on thiazide diuretics and the second comparing verapamil with labetalol in patients with coexisting chronic obstructive pulmonary disease. Both trials indicated that the 2 classes of drugs caused equivalent antihypertensive responses.

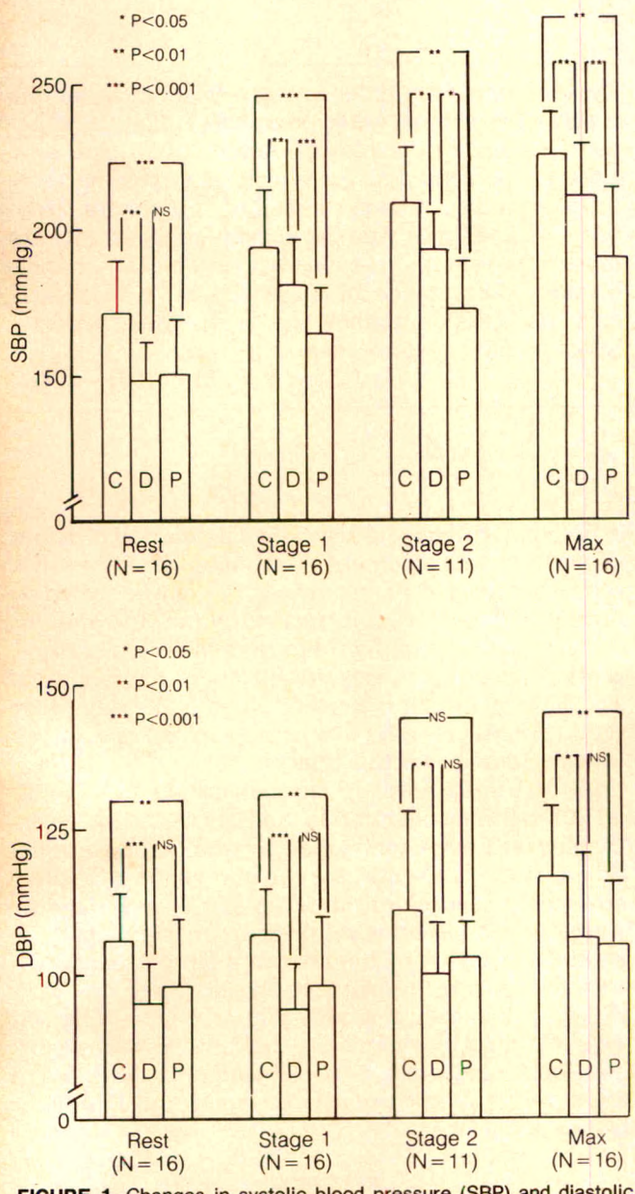

FIGURE 1. Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during treatment with placebo (C), diltiazem (D) 60 mg, 3 times a day, and propranolol (P) 20 mg, 3 times a day. The findings at rest, during submaximal exercise at the same workload (stages 1 and 2) and during maximal exercise (Max) are shown. Both drugs produced comparable responses at rest and during exercise in DBP, but propranolol was more effective in blunting the exercise-induced rise in SBP. NS = difference not significant. Reprinted with permission from Am J Cardiol.[13]

Nifedipine

Ekelund et al[9] performed an open-label trial in which 12 patients received placebo, nifedipine alone, nifedipine plus metoprolol and metoprolol alone for consecutive 1-month periods. Blood pressure was measured at rest and during exercise. Nifedipine decreased supine systolic and diastolic pressures by 20 and 11 mm Hg, respectively, compared with 22 and 7 mm Hg with metoprolol (differences not significant). During exercise, however, systolic blood pressure fell further with metoprolol than with nifedipine (39 vs 14 mm Hg). Both at rest and during exercise, nifedipine produced a slight increase in heart rate, while metoprolol significantly lowered it. Combined therapy was significantly better than single therapy, both at rest and during exercise.

Yagil et al[10] conducted a 2-phase study in which 26 severely hypertensive subjects (mean blood pressure 192/114 mm Hg on propranolol) were on a regimen consisting of nifedipine 10 to 30 mg, 3 times a day, added to propranolol. After a 14- to 30-week period of combined therapy (phase I), nifedipine and propranolol were alternatively withdrawn for 2- to 4-week periods, separated by a similar period in which the combination was reinstituted. The addition of nifedipine (mean dosage 60 mg/day) was highly efficacious, resulting in a sustained decrease in blood pressure from 189/112 to 136/84 mm Hg. During phase II, blood pressure was found to increase to pre-nifedipine levels when this drug was withdrawn. Propranolol withdrawal also resulted in a loss of control, but the blood pressure increase was significantly less than that during nifedipine withdrawal. It is noteworthy that adverse effects related to nifedipine occurred in 50% of the patients and necessitated discontinuation in 4 patients.

Two additional studies[11,12] evaluated acebutalol and nifedipine, alone and in combination, and pindolol and nifedipine, also in single and combined therapy. While both studies are limited by small numbers of patients, they each indicated equal antihypertensive efficacy for both classes of drugs, as well as added benefit from combination therapy.

Diltiazem

Diltiazem, because of its more recent development and availability, has been less widely studied in hyper-

tension. Nonetheless, there are 2 published trials, and preliminary findings from an ongoing multicenter study comparing this agent with β blockers are available. Yamakado et al[13] treated 16 subjects with mild to moderate hypertension with placebo, propranolol 20 mg, 3 times a day, and diltiazem 60 mg, 3 times a day, for 4 weeks, using a Latin square design. Resting and treadmill exercise blood pressures were evaluated (Fig. 1). At rest, both agents lowered blood pressure comparably, from a mean of 171/106 to 148/95 mm Hg with diltiazem and to 150/98 mm Hg with propranolol. Heart rate fell from 76 to 70 beats/min with diltiazem and to 59 beats/min with propranolol. During exercise, both drugs lowered diastolic pressure to a similar degree, but propranolol decreased systolic pressure somewhat more than diltiazem and caused a greater reduction in maximal heart rate. No adverse effects were noted, but the dosages of both drugs were relatively low.

Trimarco et al[14] compared diltiazem 60 mg, 4 times a day, with metoprolol 100 mg, 2 times a day, in 20 patients using a randomized, double-blind crossover design with 1-month treatment periods separated by a 1-month placebo period. Both drugs produced comparable antihypertensive effects, although metoprolol was more effective in preventing an increase in exercise systolic pressure. Only metoprolol reduced heart rate.

A multicenter trial comparing diltiazem with other agents is now in progress and will ultimately include 200 patients, thus permitting subgroup analysis based upon age and race. At present, only the findings from an interim analysis of the first 50 subjects who completed the study are available. The study design includes a 4-week, single-blind, placebo washout period, after which the patients are randomly assigned to double-blind treatment with diltiazem or propranolol. The first 3 months are a dose-titration phase in which the diltiazem dosage (in time-released form) is increased from 60 to 160 to 180 mg, 2 times a day, and propranolol is increased from 80 to 120 to 240 mg, 2 times a day, stepwise at monthly intervals. After 4 weeks at the titrated dosage, hydrochlorothiazide is added to the therapy of uncontrolled patients for an additional 8 weeks. Sixty percent of the diltiazem group and 44% of the propranolol group required the highest dose, and 32% and 40%, respectively, ultimately required the addition of diuretic. With this therapy, 59% of the diltiazem patients and 40% of the propranolol patients achieved the predetermined treatment goal of a supine diastolic blood pressure <90 mm Hg, or, in those with initial diastolic pressure of 95 to 100 mm Hg, a minimum of a 10-mm Hg reduction. In the diltiazem group, the mean supine blood pressure fell from 148 ± 17/101 ± 5 pretreatment to 133 ± 25/88 ± 9 mm Hg ($p < 0.0001$); in the propranolol group, a comparable reduction occurred from 154 ± 22/104 ± 6 to 146 ± 23/91 ± 11 mm Hg. Heart rate fell from 81 ± 24 to 74 ± 11 beats/min ($p < 0.01$) with diltiazem and from 77 ± 8 to 64 ± 11 beats/min ($p < 0.0001$) with propranolol; this was the only significant difference between treatments. The addition of hydrochlorothiazide produced a further decrease of 8 to 12 mm Hg in systolic and diastolic pressures in both treatment groups. Adverse effects and adverse reactions were generally mild and were slightly more common on propranolol (34%) than diltiazem (25%).

Calcium-Channel Blockers and Beta Blockers in Patients with Angina and Hypertension

In the U.S., calcium-channel blockers are currently used to treat hypertension primarily in patients with accompanying coronary artery disease. Frishman et al[15] studied 12 such patients with stable angina pectoris, positive treadmill exercise test results and diastolic blood pressure >90 mm Hg. After a 2-week washout period, double-blind treatment was commenced with verapamil 80 mg, 3 times a day, or propranolol 20 mg, 3 times a day, with the dosage being increased at weekly intervals to 120 mg, 4 times a day, and 80 mg, 4 times a day, respectively. The two 3-week treatment periods were separated by a 1-week placebo period. The 2 drugs produced comparable changes in blood pressure, but propranolol reduced heart rate significantly more. Both drugs reduced the frequency of anginal attacks, but exercise duration increased significantly on verapamil despite a lower rate-pressure product with propranolol.

Factors Determining the Response to Calcium-Channel Blockers and Beta Blockers

From these studies, it is apparent that both the calcium-channel blockers and β blockers are effective antihypertensive agents. Bühler et al[16] have examined the response of a large number of patients in relation to the pretreatment plasma renin activity. Their findings confirm previous reports that β blockers are most effective in high renin hypertension. In contrast, they found that calcium-channel blockers are particularly potent in low renin hypertension. Clinically, these observations are most relevant in regard to age, because younger patients tend to have higher plasma renin activity, while older patients often have low plasma renin activity. Indeed, Bühler's experience corroborates the greater efficacy of calcium-channel blockers in the elderly and β blockers in younger subjects (Fig. 2). Data are not yet available for the relative response rates of these 2 classes of agents in blacks, who usually have low plasma renin activity, and whites, who exhibit a wider spectrum of plasma renin activity.

More Trials Needed

Because of the small size of the reviewed trials, further information is needed on a number of important points. Definitive data concerning the relative efficacy of the 2 classes of agents in subgroups based on gender, race and age might help in the selection of therapy. Similar information concerning adverse effects may be equally valuable. Beta blockers have been associated with potentially adverse effects on serum lipids; calcium-channel blockers have not. Nonetheless, it would be informative to examine these measurements in a prospective comparative trial involving the same patient population and laboratory.

The greatest differences between the responses to calcium-channel blockers and β blockers in the published trials were in exercise heart rate and systolic

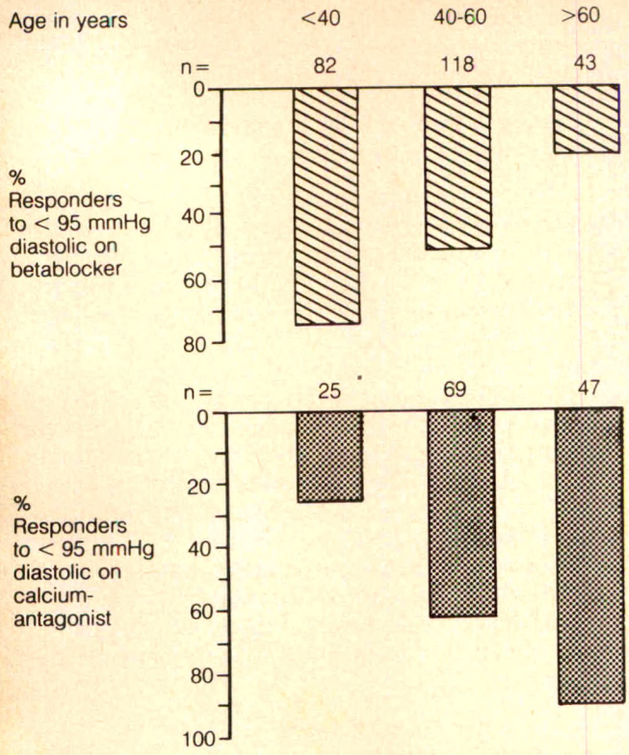

FIGURE 2. Proportion (%) of patients responding with diastolic blood pressure reduction to ≤95 mm Hg during antihypertensive therapy with β blockers and calcium-channel blockers according to their age. Reprinted with permission from Am J Med.[16]

blood pressure, which rose to a lesser extent on the latter agents. It would be interesting, then, to determine whether this is associated with actual differences in exercise performance. None of the published studies addressed this issue by measuring oxygen utilization, and several did not use the appropriate protocols to examine this question.

Clinical Implications

The studies reviewed herein indicate that the calcium-channel blockers are as effective in treating mild and moderate hypertension as β blockers, and in the case of diltiazem, they are equally or better tolerated. Because of concerns about the safety of diuretics, both classes of agents are commonly used as initial therapy in Europe. The choice of which type of medication to use in individual patients should reflect demographic factors, the patient's life-style and the nature of accompanying medical problems. Thus, in older patients calcium-channel blockers may be the most effective alternative to diuretics, whereas in young patients a β blocker or converting enzyme inhibitor should be considered. Blacks may be more responsive to calcium-channel blockers than to β blockers, although this remains to be demonstrated. When mental activity or athletic performance is an issue, calcium-channel blockers may be preferable to β blockers, because they have few central nervous system effects and they are likely to have less of a depressant effect on maximal cardiac output, although the latter point has not been investigated at the high dosages used in antihypertensive therapy or in competitive athletes. Patients with bronchospastic conditions, peripheral vascular disease, insulin-dependent diabetes and left ventricular dysfunction may be appropriate candidates for calcium-channel blockers, while those predisposed to postural symptoms or edema are better candidates for β blockers. Combination therapy with nifedipine and β blockers is safe and effective, but more experience is needed with diltiazem. Beta blocker and verapamil combinations should not be used in this way for hypertension because of the potential for atrioventricular block, bradyarrhythmias or myocardial depression.

Several additional factors will determine the future role of calcium-channel blockers in the treatment of hypertension, including their place relative to β blockers and diuretics. These include approval from the Food and Drug Administration for this indication, their relative cost, which is presently significantly higher than other antihypertensive agents, and the availability of twice-daily—or better still, once-daily—preparations. Finally, clarification of the safety of diuretics and determination of whether the calcium-channel blockers are cardioprotective will enormously influence their ultimate popularity.

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Comparative Effects of Diltiazem and Hydrochlorothiazide in Blacks with Systemic Hypertension

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The blood pressure-lowering effects of a calcium-entry blocker, diltiazem (240 or 360 mg/day), and a thiazide diuretic, hydrochlorothiazide (50 or 100 mg/day), were studied in 20 black hypertensive patients. Supine blood pressure decreases of −34/−18 mm Hg for diltiazem and −29/−21 mm Hg for hydrochlorothiazide were noted after 14 weeks of therapy. Differences between drugs were not significant. Blood pressures were normalized in all 4 of the monotherapy nonresponders when the 2 drugs were combined. Significant adverse effects were not noted.

These data suggest that diltiazem is an effective antihypertensive agent in black patients. As monotherapy, its blood pressure-lowering effect is equivalent to hydrochlorothiazide.

(Am J Cardiol 1985;56:101H–104H)

Studies have shown that black patients respond more effectively to some antihypertensive agents than to others.[1–7] This suggests the need to evaluate the effectiveness of new antihypertensive agents in black patients. Calcium-entry blockers are among the newer drugs being evaluated as antihypertensive agents. Although these agents have not yet been approved for therapy in the United States, there have been numerous reports suggesting that they are effective as blood pressure-lowering medications.[8–10]

This study was part of a multicenter trial designed to compare the antihypertensive effectiveness of diltiazem, a calcium entry–blocking agent, with hydrochlorothiazide, a thiazide diuretic, as monotherapy in patients with mild to moderate hypertension. In addition, the study assessed the effectiveness of combined therapy with both diltiazem and hydrochlorothiazide in patients who did not achieve goal blood pressure on monotherapy.

Data are reported on 20 black patients, followed for a 6-month period, on either monotherapy or combined therapy. This review includes efficacy and adverse effect data relating to therapy with both drugs.

Methods

Study design: Patients were initially evaluated in a placebo screening phase of at least 2 weeks, after a 2-week abstinence from any previous antihypertensive drug therapy or other medication known to affect blood pressure. A resting supine diastolic blood pressure of 95 to 114 mm Hg, not varying by >7 mm Hg, was required on 2 consecutive weekly visits for inclusion in the study. Baseline measurements for diastolic and systolic blood pressure and heart rate were obtained by averaging the readings taken on the last 2 visits of the placebo screening phase. Mean arterial blood pressure was then calculated from the observed diastolic and systolic blood pressure. Conduction intervals (from electrocardiogram) and automated blood chemistries, including serum lipid levels, blood counts and urinalyses, were obtained at baseline and at the end of the study.

Patients were assigned to either sustained-release diltiazem or hydrochlorothiazide in a randomized, double-blind parallel design. Titration to 240 or 360 mg of diltiazem or 50 or 100 mg of hydrochlorothiazide was carried out over an 8-week period (through week 10 of the study). Monotherapy effects were observed over 4 additional weeks (through week 14). Blood pressure measurements were obtained approximately 12 hours after the last dose of medication.

Goal blood pressure was defined as a supine diastolic blood pressure <90 mm Hg if baseline supine diastolic blood pressure was ≥100 mm Hg, or at least a 10-mm Hg supine diastolic blood pressure reduction if baseline supine diastolic blood pressure was <100 mm Hg. At week 14, those patients who had achieved goal blood pressure were continued on the assigned monotherapy, either diltiazem or hydrochlorothiazide, for an additional 12 weeks. If a patient had not achieved goal by week 14, he or she was "unblinded" and the alternate drug was added to the original regimen for an additional 12 weeks. The study was designed to simulate a clinical situation in which additional therapies are added if monotherapy is ineffective.

Three groups resulted for analysis: subjects who achieved goal blood pressure with diltiazem and who continued on diltiazem; subjects who achieved goal with hydrochlorothiazide and continued on hydrochlorothiazide; and subjects

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TABLE I Characteristics of Study Patients

	Diltiazem	Hydrochlorothiazide
Male (n)	0	2
Female (n)	10	8
Average age (years)	54.9 ± 10.4	54.3 ± 9.3
Weight (lb)	156.9 ± 22.3	173.3 ± 33.1
Supine DBP (mm Hg)	104.5 ± 3.0	103.4 ± 4.1
Supine SBP (mm Hg)	165.4 ± 17.9	154.6 ± 10.9
Supine MAP (mm Hg)	124.8 ± 6.3	120.5 ± 5.6
Supine HR (beats/min)	76.9 ± 8.1	73.2 ± 9.7
Standing DBP (mm Hg)	102.0 ± 4.8	102.0 ± 6.1
Standing SBP (mm Hg)	158.1 ± 19.0	144.0 ± 9.1
Standing MAP (mm Hg)	120.7 ± 8.6	116.0 ± 5.4
Standing HR (beats/min)	80.7 ± 7.7	76.6 ± 10.5

DBP = diastolic blood pressure; SBP = systolic blood pressure; MAP = mean arterial pressure; HR = heart rate.

who did not achieve goal with either diltiazem or hydrochlorothiazide and were consequently followed on combination therapy. (Two patients were continued on monotherapy, 1 on each drug, beyond week 14 even though goal blood pressure was not achieved.)

Standard statistical methods (paired *t* test, analysis of variance, Fisher's exact test) were used to determine significance of blood pressure decreases and goal responders for the 2 monotherapy groups at 14 weeks. Analysis at week 26 included a comparison of 3 groups: those receiving diltiazem only, those receiving hydrochlorothiazide only and those receiving both drugs.

Results

Table I summarizes the demographics and baseline blood pressures in the 2 groups of patients receiving monotherapy. Mean blood pressures were somewhat higher in the group randomized to diltiazem.

Table II summarizes the number and percentage of patients achieving goal pressures on monotherapy and combined therapy. At week 14, 7 of 9 patients responded to diltiazem alone and 6 of 10 patients had reached goal with hydrochlorothiazide (differences not significant). At week 26, 6 of 8 patients on diltiazem were at goal pressure, whereas all patients on hydrochlorothiazide or receiving combined therapy had achieved goal pressure.

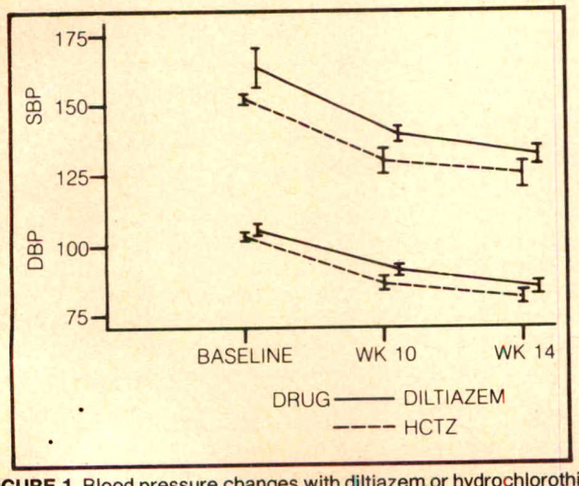

FIGURE 1. Blood pressure changes with diltiazem or hydrochlorothiazide (HCTZ) as monotherapy. All patients were in resting supine position. DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table III summarizes supine blood pressure changes in *all patients* on monotherapy at weeks 10 and 14. A decrease of −34/−18 mm Hg from baseline was noted at week 14 with diltiazem, and a decrease from baseline of −29/−21 mm Hg with hydrochlorothiazide. These are equivalent clinical responses, showing no statistically significant differences. Figure 1 shows blood pressure differences noted over the course of the study with both drugs.

Results of supine blood pressure changes in the *goal achievers* on hydrochlorothiazide or diltiazem monotherapy over the 6-month duration of the study are noted in Table IV. Initial decreases in pressures from baseline to week 14 were −32/−19 mm Hg for diltiazem and −35/−27 mm Hg for hydrochlorothiazide. These responses were maintained with only slight changes for the duration of the study (through week 26). Again, there were no statistically significant differences between drugs.

The 4 patients requiring combination diltiazem and hydrochlorothiazide after week 14 achieved an additional blood pressure response of −11/−10 mm Hg at week 26 (Table V). All of these patients achieved goal response.

Upright blood pressure responses (immediately upon standing and 5 minutes after standing) were essentially similar to those noted in the supine position. At week 14, patients taking diltiazem showed a greater blood pressure decrease on standing than did those taking hydrochlorothiazide. The increases seen in heart rate on standing in the respective drug groups were not significantly different.

Electrocardiogram analysis: Electrocardiograms were taken during the first preplacebo visit and at 26 weeks, and were examined for changes in PR, QRS and QT intervals. Although the differences found are probably not of clinical significance, the diltiazem monotherapy group showed a statistically significant decrease in the QRS interval from 0.077 to 0.065 seconds at week 26 and a statistically significant increase in QT interval from 0.37 to 0.39 seconds. The combination therapy group showed a statistically significant increase in PR interval from 0.19 to 0.20 seconds. No other significant changes were noted.

Adverse effects: Patients reported few adverse effects throughout the study. One patient receiving diltiazem complained of a headache, which resolved with continued therapy. The laboratory findings on diltiazem showed no significant effects on serum electrolyte levels. Serum potassium levels decreased from a mean of 4.1 to 3.9 mEq/liter and uric acid levels increased from 5.1 to 5.6 mg% in the hydrochlorothiazide group. Statistically significant changes in lipid levels were not noted with either drug, although cholesterol levels decreased over the course of the study with both drugs (263 to 235 mg% with diltiazem, and 231 to 204 mg% with hydrochlorothiazide).

Discussion

Previous studies have demonstrated that black patients do not respond as well as whites to propranolol,[1] nadolol,[2] atenolol,[3] pindolol[4] or captopril.[5–7] In each of the above trials, blacks responded as well as or better

TABLE II Number of Patients Achieving Goal Blood Pressure

	Week 10	Week 14		Week 22	Week 26
Diltiazem	4 of 10 (40%)	7 of 9 (78%)	Diltiazem only	4 of 8 (50%)	6 of 8 (75%)
			Hydrochlorothiazide and Diltiazem	2 of 4 (50%)	4 of 4 (100%)
Hydrochloro-thiazide	5 of 10 (50%)	6 of 10 (60%)			
			Hydrochlorothiazide only	7 of 7 (100%)	7 of 7 (100%)

TABLE III Supine Blood Pressure (mm Hg) Changes in All Patients on Monotherapy with Diltiazem or Hydrochlorothiazide*

	Baseline	Week 10	Week 14	Difference (Baseline − Week 14)
Diltiazem	165/104	140/91	133/86	−34 (p = 0.0002) −18 (p = 0.0001)
Hydrochloro-thiazide	154/103	129/87	125/82	−29 (p = 0.0003) −21 (p = 0.0002)

* There were no statistically significant differences between drugs.

TABLE IV Supine Blood Pressure (mm Hg) in Responders After Monotherapy with Diltiazem or Hydrochlorothiazide*

	Baseline	Week 14	Week 26	Difference (Baseline − Week 26)	Difference (Week 14 − Week 26)
Diltiazem	166/105	134/86	138/85	−28 (p = 0.0051) −20 (p = 0.0001)	+4 (NS) −1 (NS)
Hydrochloro-thiazide	156/105	121/78	125/81	−31 (p = 0.0027) −23 (p = 0.0001)	+4 (NS) +3 (NS)

* There were no statistically significant differences between drugs.
NS = not significant.

than whites to hydrochlorothiazide, chlorthalidone and bendroflumethiazide. When any 1 of these diuretics was combined with propranolol, nadolol or captopril in these studies, the racial differences were abolished and goal blood pressure responses were noted in a high percentage of patients.

Labetalol[11] appears to work as well in blacks as in whites. Data indicate that nitrendipine,[12] a new calcium-entry blocker related to nifedipine, is also effective in black patients. The present study suggests that there is little difference in the blood pressure response in blacks between hydrochlorothiazide in dosages of 50 or 100 mg and diltiazem in dosages of 240 or 360 mg/day when given as monotherapy. Further, the magnitude of blood pressure reduction was significant, and goal blood pressure was achieved in a majority of patients.

It has been suggested that baseline renin status or the relative levels of activity of the kinin or other vasodilator systems may play a role in and at least partially explain the racial differences in response to different antihypertensive medications. Beta-adrenergic inhibitors and converting enzyme inhibitors[13] are less effective in patients with low baseline plasma renin levels, and hypertensive blacks as a group tend to have lower plasma renin activity than whites. Black patients also tend to have a less active kinin system. Labetalol, an α antagonist as well as a β-adrenergic blocking agent, may be less affected by renin status, and the action of diltiazem and other calcium-entry blockers, by virtue of their direct vasodilating effects, may also be less influenced by the activity of the renin-angiotensin system. It has also been suggested that calcium-entry blockers are more effective in the elderly, another group of patients in whom resting low renin levels are noted with relatively high frequency.

Blaustein and Hamlyn[14] have offered a unifying hypothesis for sodium-calcium exchange and hypertension based on natriuretic hormones. This predicts that blacks and other patients with low renin hypertension would respond particularly well to calcium-entry blockers.

A preliminary report[15] suggests that methyldopa is effective in reducing the blood pressure of black patients who have an increase ≥5 mm Hg in diastolic blood pressure upon standing. Fifteen of 23 patients with an orthostatic increase showed a reduction of 15.4 ± 12.2 compared with only 1.6 ± 11.5 mg Hg for those 8 without an orthostatic increase. The dosage ranged from 250 to 1,000 mg, 2 times a day. Hydrochlorothiazide at 25 to 50 mg, 2 times a day, achieved a greater overall quantitative blood pressure reduction (−17 vs −11 mg Hg), but results did not correlate with orthostatic change. This suggests that differences in base-

TABLE V Supine Blood Pressure (mm Hg) in Nonresponders After Combined Therapy (Diltiazem and Hydrochlorothiazide)

Week 14 (End of Monotherapy)	Week 26	Difference (Week 14 − Week 26)
138	127	−11 (p = 0.0502)
92	82	−10 (p = 0.0042)

line sympathetic tone in black patients could account for differences in response and might explain some of the differences among studies.

The reasons for the observed racial differences in response to various drugs have not been identified with certainty. Multiple factors are likely to be responsible and they have been reviewed elsewhere.[1,16]

Whatever the underlying mechanisms, physicians should be aware of the potentially different effects of antihypertensive agents in different racial groups. A more rational approach to therapy may therefore be planned. The present study comparing the blood pressure-lowering effects of diltiazem and hydrochlorothiazide in a small group of black patients suggests that an equivalent response can be expected when the drugs are used as monotherapy. An additional blood pressure-lowering effect occurs when the drugs are combined in standard clinical dosages.

In summary, diltiazem at 240 or 360 mg/day appears to be as effective an antihypertensive agent as hydrochlorothiazide at 50 or 100 mg/day in black patients with mild to moderately severe hypertension. There were no significant blood pressure differences between the 2 drugs as monotherapy when changes from baseline were compared at the end of week 14 and week 26. When the 2 drugs were combined in those who did not respond to monotherapy, a further statistically significant decrease in blood pressure was obtained. These data suggest that diltiazem as monotherapy is an effective antihypertensive agent in black patients and may also be useful in combination with a diuretic. Significant adverse effects were not noted with either drug, but diltiazem produced a greater decrease in standing blood pressure. There was no evidence that diltiazem alone adversely affected cardiac conduction or arrhythmias, although a statistically significant increase in QT interval was noted (0.02 seconds). PR interval was slightly increased in the group receiving both drugs (0.01 seconds).

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Individualization of Calcium Entry–Blocker Dosage for Systemic Hypertension

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The calcium entry blockers are used in a wide variety of clinical situations. Coexisting disease states, such as renal or hepatic dysfunction, may require individualized dosing of these agents. The physiologic changes associated with aging may also affect the pharmacokinetic properties of the drugs. If calcium entry blockers are used concurrently with other medications, dosage adjustment or selection of an alternative drug may be needed. Drug interactions between calcium entry blockers and cimetidine, digoxin and quinidine appear to be clinically significant. Individualized dosing in patients who have coexisting disease or who are using other medications is essential to achieve an adequate therapeutic response and avoid adverse effects. Considerations to attain an optimal response in such situations are presented.

(Am J Cardiol 1985;56:105H–111H)

The calcium entry–blocking drugs have been used in the therapy of arterial hypertension for a number of years.[1–3] There are 3 drugs of this class currently available in the United States (Table I) and each has a unique pharmacokinetic profile. Moreover, these drugs differ markedly from some of the currently used antihypertensive agents. The differences both among the calcium entry blockers and between them and conventional therapies are important, because these drugs are playing a role in antihypertensive therapy. An appreciation of the pharmacokinetic characteristics, the dosage modification required in selected disease states and the drug interaction profiles for each of these agents should be useful in achieving optimal therapy in the individual patient.

Pharmacokinetic Parameters

The general pharmacokinetic parameters for the currently available calcium entry blockers are listed in Table I. All 3 drugs are readily absorbed from the conventionally used oral dosage form and attain maximal plasma concentrations within 30 to 180 minutes.[4] They each undergo a significant presystemic elimination (first-pass effect), with verapamil exhibiting a greater presystemic loss (and lower bioavailability) than the other 2 agents.[6–8] Because most of the bioavailability studies performed with these drugs have been done in fasting subjects, there is no information available on the effect of food on this parameter. However, it is possible that the concurrent administration of either a carbohydrate-rich or protein-lipid meal would decrease the extent of first-pass metabolism, as has been demonstrated for propranolol.[9] Therefore, patients are best advised to take these medications either on any empty stomach or before meals to ensure consistency in bioavailability (even though it is possible that a decreased quantity of the active drug moiety reaches the system under these conditions).

All 3 drugs are extensively distributed to most tissues, including the central nervous system. Plasma protein binding of diltiazem and verapamil is independent of concentration over the range of clinically used plasma concentrations;[10,11] thus, no clinically significant drug displacement interactions are anticipated for these agents. Studies with diltiazem have demonstrated a lack of displacement when administered concomitantly with various other compounds—for example, warfarin, propranolol and digoxin.[11] On the other hand, plasma protein binding of nifedipine has been shown to be concentration dependent,[12] but no clinically significant displacement interactions have been reported to date.

The elimination of these agents is primarily handled by hepatic microsomal oxidases with subsequent renal elimination of various metabolites,[4] although 3 to 4% of a dose of verapamil is eliminated in unchanged form. The half-lives of all 3 drugs are similar after a single oral dose. However, the half-life of verapamil has been shown to double after long-term oral dosing [5,13–15]—for example, from 5.7 to 9.6 hours in normal patients[13] and from 6.4 to 12 hours in patients with chronic atrial fibrillation.[15] Thus, in long-term

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TABLE I Pharmacokinetic Parameters of Calcium Entry Blockers[4-8]

	Diltiazem	Nifedipine	Verapamil
Oral absorption (%)	>90	>90	>90
Bioavailability (%)	41–67	37–68	10–22
Protein bound (%)	77–80	92–98	83–92
Therapeutic plasma concentration (ng/ml)	40–200	25–100	80–300
Elimination pathway	Hepatic	Hepatic	Hepatic/Renal
Active metabolites	O-desacetyldiltiazem (40 to 45% activity of parent compound)	None	Norverapamil (10% activity of parent compound)
Elimination half-life (hours)	2.1–5.8	1.9–5.8	2.8–6.3*

* Increased with chronic dosage.

TABLE II Effect of Various Physiologic States on Calcium Entry-Blocker Dosage

	Diltiazem	Nifedipine	Verapamil
Pediatric	Not approved—no clinical data available	Not approved—no clinical data available	0.1 mg/kg intravenous (for a maximum total of 3 doses) 240–360 mg/daily, oral
Geriatric	Reduce oral dose by approximately 25% in patients >70 years; titrate slowly, beginning with low dose	No data available, but presumably similar to diltiazem	No data available, but oral or intravenous dose should be reduced by at least 50% for initial dose and titrated slowly
Liver disease	Reduce initial oral dose by 30 to 40% in severe liver disease and titrate slowly with close supervision	No data available, but presumably similar to diltiazem	Initial doses should be 1–3 mg intravenous or 80–120 mg/day oral; monitor closely
Renal disease	No dosage adjustment needed	Pharmacokinetic parameters unchanged, but pharmacologic response significantly enhanced	Avoid use, but if essential, reduce dosage consistent with reduction in creatinine clearance
Diabetes mellitus	Appears to be safe, but should be closely monitored at first	Use caution; conflicting reports in clinical studies	Appears to be safe, but should be closely monitored at first

oral therapy, the dosage interval for verapamil may be extended to 8 or, in some individuals, 12 hours. Similarly, because the shift in half-life and the correlated increase in the area-under-the-plasma-concentration curve occur within the first few days of dosing, dosage escalation should not be undertaken until the patient is assessed at the steady-state plasma concentration; this usually occurs 4 to 5 days after drug initiation. Dose-related changes in the bioavailability of diltiazem have been reported, but the differences are not as pronounced as those of verapamil.[16] It appears that the presystemic elimination of diltiazem is saturable, so that larger doses will result in enhanced bioavailability and subtle increases in half-life.[17] Clinical dosage modification is not required but practitioners should be aware that larger individual oral doses will give a slightly greater response than might be estimated on a strict proportional basis.

The relatively short half-life of the calcium entry blockers might provoke concern regarding the physiologic consequences of abrupt discontinuation. However, studies in patients with unstable angina,[18] variant angina,[19] chronic stable angina[20] and hypertension[21] have shown no withdrawal symptomatology. In contrast, there are 2 reports that describe potential withdrawal symptoms with these drugs. Bala Subramanian et al[22] have described 5 angina patients who developed symptomatology that was suggestive of drug withdrawal upon discontinuation of verapamil and diltiazem. Changes in the ST segment and tachycardia were noted; however, only 2 of the 5 patients actually reported any problem. The inhibitory actions of the calcium entry blockers on sympathetic activity have been proposed as a possible basis for these withdrawal symptoms.[22,23] In a subsequent report, Engelman et al[24] described 4 patients who underwent coronary revascularization surgery after abrupt withdrawal of either nifedipine or diltiazem. Severe coronary vasospasm resulted and was confirmed in 3 of the 4 patients by ST-segment changes in the electrocardiogram. Sublingual nifedipine and intravenous nitroglycerin were effective in ameliorating signs of ischemia in 2 patients; but both of the other patients developed infarcts, and 1 died despite heroic resuscitative measures. It is recommended that patients on long-term calcium entry–blocker therapy be maintained on the medication for 24 to 48 hours postoperatively. If a calcium entry blocker is to be discontinued, a conservative approach would involve decreasing the oral dose by 30 to 35% every 4 to 5 days for a period of 2 weeks, with careful monitoring for any signs of cardiovascular rebound.

Use in Selected Patients

In contrast to certain antihypertensive medications, the calcium entry blockers can be used safely in the majority of patients with concurrent migraine headache,[25] bronchial asthma[26,27] or angina. However, there are a number of clinical situations in which dosage adjustment may be considered (Table II).

Pediatrics: Pediatric use of medications that are conventionally prescribed for adults often calls for significant dosage adjustment. Verapamil has been used in pediatric patients for the treatment of supraventricular tachycardia.[28] Hypotension was noted after "a large dose of the drug," so 0.1 mg/kg was infused intravenously over a 30-second period, with a maximum of 2 additional doses if hypotension did not limit dosing. If extrapolated for body weight, this dosage is equivalent to an individual dose of 7 mg in a 70-kg individual, which is similar to the recommended adult dosage (5 to 10 mg). Oral dosages of 80 to 120 mg, 3 times a day, are also used in children, and this range is also quite close to the adult dosage for the drug. Thus, pediatric use of the intravenous preparation should be based on individual body weight, but oral dosing may be used in the lower range of commonly used adult doses.

Lactation: The authors of the previous study noted that verapamil is useful in the treatment of paroxysmal supraventricular tachycardia in children of all ages, but that it may not be effective in infants under 6 months of age.[28] Nonetheless, the presence of the drug in milk poses 2 potential hazards to the nursing infant —cardiovascular depression and hepatic damage owing to hypersensitivity.[29] The former is presumably related to dose; the latter is not. Andersen[30] reported that the average concentration of verapamil in milk is 23% of the maternal serum level, resulting in a serum level of 2.1 ng/ml in the infant. Although this level of verapamil would not be expected to result in depressed cardiovascular function, hypersensitivity reactions could still occur in the infant. In contrast, Inoue et al[31] noted that the levels of verapamil in the mother's serum and milk were essentially equivalent, raising the projected plasma concentration in the infant to 20 ng/ml. Because the concentration of verapamil in nonionized form is quite high, similar concentrations of verapamil would be expected in maternal serum and milk. Thus, the data of the latter study are more in keeping with calculated projections. Until further studies are done to determine the actual excretion rate of this drug into human milk and the effects of such an exposure on the infant, it is best for women using verapamil to avoid breast feeding. The lack of studies of this type for diltiazem and nifedipine also precludes their use in nursing mothers.

Geriatrics: Because of the apparent microsomal oxidation of these drugs by the liver, the changes in both hepatic drug oxidation[32] and hepatic blood flow[33] noted during the aging process may call for conservative dosing in elderly patients.[34] In a study done with diltiazem in elderly subjects (64 to 75 years), absorption rate appeared to be reduced and half-life was prolonged from 6.6 ± 0.13 hours in 20 to 30-year-old control subjects to 10.9 ± 0.93 in elderly patients.[35] However, there was no change in the bioavailablity of the drug. Although these data are of interest, further studies are needed—particularly because this study evaluated only 3 patients. In general, information regarding the use of calcium entry blockers in the elderly population is lacking. Until more data are available, the tenet, "start low, go slow," should apply to the use of these agents in patients over 70 years of age, considering the potential compromise in hepatic metabolism associated with aging.

Liver disease: All 3 of the currently available calcium entry blockers are extensively metabolized by the liver (Table I). Therefore, liver disease would most certainly have the potential to modify the pharmacokinetic parameters of those agents, with a resultant increase in half-life. Studies with verapamil have demonstrated that clearance may be reduced by approximately 50% and half-life increased to 4 times that of normal controls.[36] Bioavailability was found to be 52.3% compared with 22% in control volunteers. These researchers suggest that cirrhotic patients should receive half of the normal intravenous dose of verapamil or 20% of the normal oral dose in order to avoid untoward effects. Woodcock et al[37] found considerable variation (3.8 to 64%) in the bioavailability of verapamil in subjects with liver disease, and recommend a dosage reduction to 33% of the normal dose. They stress that there is considerable interpatient variation and that some cirrhotic patients may have a "bioavailability actually lower than normal." [38] Subsequent studies in patients with Laennec's cirrhosis have shown decreased plasma protein binding of verapamil in this population in association with a lower concentration of binding proteins. In these patients, higher steady-state levels of verapamil could be anticipated after intravenous, but not oral, administration.[39] Thus, for cirrhotic patients, an intravenous dosage recommendation of 50% of the normal dose is appropriate, as is a recommendation of cautious escalation of oral dose starting from 25% of the normal oral regimen. Because of their significantly higher bioavailability, nifedipine and diltiazem would not be presumed to demonstrate such marked changes in the presence of hepatic disease; however, a cautious approach to dosage increase with these agents is still indicated.

Renal disease: Reports regarding the use of either verapamil or diltiazem in patients with renal disease have identified differential dosing recommendations for these agents. Patients with advanced renal disease who had received either intravenous or oral verapamil showed a significant decrease in apparent volume of distribution, elimination half-life and total body clearance.[40] The renal clearance of verapamil was significantly decreased from 0.38 to 0.004 ml/min/kg after intravenous doses. This was accompanied by a significant decrease in total clearance from 12.08 to 5.33 ml/min/kg. Thus, dosages of verapamil should be lowered significantly in uremic patients as well as in elderly patients in whom renal function may be compromised. In contrast, Pozet et al[41] found that both diltiazem and its main metabolite, desacetyldiltiazem, had similar pharmacokinetic profiles in patients with "severely impaired renal function" and in normal patients. Although this contrast between diltiazem and verapamil may seem difficult to explain, one should consider that 3 to 4% of a dose of verapamil is excreted unchanged,[4] and this may indicate that as much as 30 to 40% of the active drug is absorbed. Diltiazem, on the other hand, has high bioavailability (approximately

50%) and less than 1% is excreted unchanged; approximately 2% of the absorbed dose was found in the urine. Although data are unavailable, nifedipine should have a profile similar to that of diltiazem, but caution should be observed with this drug until studies are performed.

Diabetes mellitus: Verapamil reduces insulin release in vitro in response to both glucose and sulfonylureas.[42] Because of this finding, there may be some concern regarding the use of these agents in the diabetic patient. Rodjmark and Andersson[43] found that both oral and intravenous verapamil actually improved tolerance to orally administered glucose in type II diabetics and had no effect on therapy with glibenclamide. There was also no effect on both glucose tolerance and release in normal individuals. Diltiazem therapy over an 8-day period showed no effect on plasma glucose, insulin or glucagon concentrations.[44] Thus, it would appear that use of diltiazem should also be safe in diabetic patients, although trials have not been done in this specifc population. In contrast, there are equivocal findings regarding nifedipine usage. There are reports of impaired glucose tolerance,[45] reduced insulin secretion and inhibition of glucagon suppression[46] in noninsulin-dependent diabetics; however, other studies have not been able to support these findings.[47] Similarly, in insulin-dependent diabetics, nifedipine administration caused no change in plasma C peptide concentration.[48] Thus, although use of both verapamil and diltiazem seems safe in the diabetic patient, caution should be exercised in the administration of nifedipine until further documentation is available.

Drug Interactions

Calcium entry blockers may interact with other drugs via either pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic drug interactions are not discussed here in any detail, because the only ones that have been described in the clinical literature are obvious due to their synergistic nature—for example, the additive cardiodepressant actions of verapamil with disopyramide. Because of the potential atrioventricular nodal depression associated with both diltiazem and verapamil, caution should be used if patients are on therapy with disopyramide, quinidine, procainamide or other antiarrhythmic agents; if possible, these combinations should be avoided. Concomitant use of β blockers has been addressed in another article in this issue;[49] existing data indicate that the combination of calcium entry blockers and β blockers can be tolerated safely in most patients. More caution is required in the use of verapamil and diltiazem, and β-blocker dosage should be decreased to approximately 50% of the baseline dose during combination therapy. It is probably best to avoid the use of the intravenous form of verapamil in patients taking β blockers. If this latter combination is to be used, it is best to discontinue propranolol 24 hours before administering verapamil or to wait 12 to 24 hours after discontinuance of intravenous verapamil to initiate β-blocker therapy. However, if it is deemed clinically essential to use such a combination, the patient should be monitored closely and cardiovascular supportive measures must be readily available.

Several pharmacokinetic drug interactions (Table III) have been reported for calcium entry blockers. Many of these can be ascribed to the extensive hepatic metabolism of these drugs, but their clinical relevance remains to be evaluated. However, when other agents metabolized by the microsomal oxidative system are used concurrently, the practitioner should be aware of potential interactions for either drug.

Cimetidine: Cimetidine, a widely used agent for gastrointestinal disorders, has been shown to reduce hepatic blood flow and inhibit hepatic microsomal oxidative function.[50] When either oral or intravenous verapamil was administered to patients taking cimetidine (1,200 mg/day), oral bioavailability was increased from 26.3 to 49.3%. Despite this pronounced change in bioavailability, which was accompanied by a 39% decrease in clearance, the investigators noted that there was no significant change in PR interval and concluded that "in a patient taking oral verapamil, cimetidine would be unlikely to precipitate atrioventricular nodal conduction block."[51] This finding must be cautiously interpreted, because the investigators used a single-dose methodology in verapamil administration and evaluation. If the drug were given chronically with cimetidine, there would be a chance for greater accumulation because of the increase in half-life associated with long-term dosing.[5,13–15] Thus, patients using these 2 drugs simultaneously should be closely monitored for hypotension, constipation, atrioventricular nodal depression and other dose-related adverse effects. If these reactions occur, the dosage of verapamil should be reduced. In another study, 6 normal subjects were given 40 mg/day of nifedipine for 1 week with 1,000 mg/day of cimetidine, or nifedipine alone in a crossover protocol.[52] An 80% increase in area-under-the-plasma-concentration-time curve and in maximal plasma concentration was reported during concurrent therapy. Plasma clearance of nifedipine was reduced by 40% in the presence of cimetidine. When ranitidine was administered concomitantly with nifedipine, there were no significant effects on the calcium entry–blocker concentration (although a slight increase in plasma nifedipine levels was noted). In an additional study of 7 hypertensive patients, cimetidine administration resulted in a significant exacerbation of the hypotensive adverse effects of nifedipine dosing. Thus, if therapy is needed for concurrent ulcer disease in a patient requiring calcium entry–blocker therapy, it is best to use either ranitidine or sucralfate; neither of these agents has been shown to interact with calcium entry blockers.

Smoking: Cigarette smoking has been shown to stimulate both the heart rate and the activity of hepatic microsomal oxidases. These effects would be antagonistic to the action of any antianginal agent, because increased heart rate increases myocardial oxygen demand, while increased drug metabolism results in lower plasma levels of the drug compared with

those of a nonsmoker. In a study comparing the effects of smoking on the antianginal actions of propranolol, atenolol and nifedipine, it appeared that smoking had the greatest antagonistic effect on nifedipine, because patients showed the greatest improvement after cessation of smoking while taking this agent.[53] However, the interaction appeared to be more of a pharmacodynamic rather than a pharmacokinetic antagonism, because plasma levels of nifedipine did not differ significantly during the smoking and nonsmoking phases of the study.

Digoxin: Although all 3 of the currently available calcium entry blockers have been shown to interact with digoxin, the nature and intensity of the interaction vary from drug to drug. In a study with diltiazem, subjects received a single oral dose of 0.5 mg digoxin in the presence or absence of 1-week pretreatment with 90 mg/day diltiazem. Diltiazem was found to increase the plasma levels of digoxin 3 to 12 hours after digoxin dosing with a concomitant decrease in oral clearance from 3.05 to 2.31 ml/min/kg. There were no significant changes in absorption, peak concentration time, distribution half-life, elimination half-life or apparent volume of distribution.[54] A subsequent study with diltiazem at 180 mg/day indicated that digoxin half-life was prolonged from 36.7 to 44.5 hours during combination therapy.[55] Total digoxin clearance was decreased by 26.9%, although renal clearance did not decrease significantly (16.25% reduction). Digoxin had no effect on the pharmacokinetic parameters of diltiazem. The combined use of diltiazem and digoxin should be avoided in patients being maintained at plasma digoxin concentrations >1.5 ng/ml and in patients with known renal dysfunction. Caution should be used in elderly patients, and therapy with diltiazem in digitalized patients should be initiated with close observation for signs of toxicity.

There are conflicting clinical reports regarding the the interaction of nifedipine with digoxin. An initial report indicated that nifedipine at 30 mg/day for 2 weeks would increase the plasma digoxin level by 45%.[56] However, a subsequent study noted that nifedipine actually increased the extrarenal clearance of digoxin and had no significant effect on renal digoxin clearance, distribution or elimination half-life.[57] This latter study was criticized because of the use of an intravenous challenge with digoxin rather than the conventional oral therapy; however, subsequent studies have demonstrated that concurrent administration of oral nifedipine had no effect on levels of digoxin in either normal subjects[58] or cardiac patients.[59,60] Thus, it would appear safe to use this drug in digitalized patients, but good clinical practice dictates that the initiation of any new medication in the cardiac patient requires careful assessment and monitoring.

In a number of clinical studies, verapamil has been found to have pronounced effects on the pharmacokinetics of digoxin. Klein et al[61] initially reported a 69% mean increase in serum digoxin levels when verapamil (240 mg/day) was administered concurrently. Subsequent studies have shown similar increases in serum digoxin concentration associated with concomitant verapamil dosing in both healthy volunteers[56,62] and patients with chronic atrial fibrillation.[63] In the latter study, in which 49 patients were evaluated, plasma digoxin levels rose from 0.76 to 1.31 ng/ml when concomitant therapy with verapamil (240 mg/day) was used. Doses greater than 240 mg/day had no more significant effect, but the increase in serum digoxin was dose-dependent up to that level. Maximum digoxin concentrations were noted 1 week after initiation of verapamil and returned to baseline 2 weeks after the last dose of the drug. Three mechanisms have been postulated to explain the basis of this drug interaction: decreased renal digoxin clearance,[62] decreased nonrenal digoxin clearance[62] and decreased volume of distribution for digoxin.[63] Further research is needed to assess the contribution of each of these potential mechanisms. The clinical relevance of this interaction is pointed out in the initial studies done by Klein et al,[61] in which 7 of 49 patients receiving combination therapy with verapamil and digoxin had signs of digoxin intoxication. In a more recent report, Zatuchni[64] described 2 patients (73 and 77 years old) with a history of cardiac disease who received either oral or intravenous verapamil while being maintained on digoxin. After 7 days of combination therapy, levels of serum digoxin peaked at 4 ng/ml, and both patients died. If a patient is to be maintained on a combination regimen of this type, digoxin dosage should be reduced by 50%, and frequent serum digoxin measurements should be taken to avoid toxicity.

Quinidine: Although the potential pharmacodynamic interaction between verapamil (and, possibly, diltiazem) and quinidine has been mentioned previously, a pharmacokinetic interaction apparently occurs between nifedipine and quinidine in some patients. Farringer et al[65] reported 2 cases in which con-

TABLE III Pharmacokinetic Drug Interactions with Calcium Entry Blockers

Drug	Calcium Entry Blocker	Recommendations
Cimetidine	Diltiazem, verapamil, nifedipine	Reduce dosage by 50% initially and titrate slowly or use ranitidine or sucralfate
Digoxin	Diltiazem	If digoxin level is >1.5 ng/ml, use with extreme caution and monitor closely; reduce digoxin dose as needed
Digoxin	Nifedipine	Appears to be safe, but monitor closely and reduce digoxin dosage if needed (see text)
Digoxin	Verapamil	Reduce digoxin dosage by 33 to 50% and monitor carefully
Quinidine	Nifedipine	Serum quinidine concentrations may be markedly lowered in the presence of nifedipine; if this occurs, discontinue nifedipine and monitor for rebound increase in serum quinidine

current nifedipine therapy appeared to decrease serum quinidine levels. Discontinuation of nifedipine therapy resulted in an increase in serum quinidine concentration from 2 to 2.5 to 4.6 μg/ml in one case and from 1.7 to 4 μg/ml in the other. Thus, this combination should be used with caution, particularly because of the rebound increase in serum quinidine levels after nifedipine is discontinued. Similarly, if adequate serum concentrations of quinidine cannot be attained, concurrent nifedipine administration should be ruled out as a cause of this problem before larger quinidine doses are ordered.

At present, there is no clinical documentation to support the notion that other drugs may interact with the calcium entry blockers. However, the practitioner should keep in mind the possibility of interactions with such other agents as antidiabetic medications, agents that affect microsomal oxidative metabolism (e.g., disulfiram) and agents that have been shown to inhibit calmodulin (phenothiazine antipsychotic drugs or tricyclic antidepressants are examples of such agents). Each of these agents possesses the mechanistic potential to affect the response to calcium entry blockers.

In summary, there are a number of clinical situations in which the dosage of calcium entry blockers must be modified. Tables II and III summarize them. In most of these situations, it is still possible to achieve an optimal response to the calcium entry blocker if dosage is modified accordingly. However, as in all clinical situations, the practitioner must not only modify dosage, but should also monitor the patient more frequently for potential adverse reactions.

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A Symposium:
Transdermal Nitroglycerin—Maximizing Therapeutic Efficacy

Editor:
William H. Frishman, MD

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A Symposium: Transdermal Nitroglycerin—Maximizing Therapeutic Efficacy

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A Symposium: Transdermal Nitroglycerin—Maximizing Therapeutic Efficacy

Introduction

WILLIAM H. FRISHMAN, MD

Nitroglycerin is the oldest pharmacotherapy for the treatment of angina pectoris. In addition to sublingual nitroglycerin, longer-acting preparations are available to provide angina prophylaxis. The most recent formulation of nitroglycerin devised to provide long-acting effect is the transcutaneous sustained-release patch. Since its introduction in 1981, transdermal nitroglycerin has gained wide acceptance in the clinical community. Recently, however, questions have arisen regarding the most efficacious use of transdermal patches. The clinical situations in which patches may best be used and the manner in which they should be administered have emerged as pivotal issues and are now being evaluated. In July 1985, a symposium was held in New York, New York, to discuss the nitrates and to update the available knowledge on the utility of the transcutaneous formulation. This symposium supplement reports on these proceedings.

The symposium Chairman, Dr. Stephen Scheidt, began with an update on transdermal nitroglycerin that included a detailed and critical overview of the clinical trials that have been conducted using transdermal patches. Dr. Scheidt emphasized that differences in protocol design currently make it impossible to reach firm conclusions about the true clinical role of the patches in the long-term management of angina, but noted that there is definitely an indication that the patches are effective in certain clinical situations.

This author then provided an overview of the pharmacology of nitrates, which included their mechanism of action and clinical pharmacology. Dr. Jan Weber followed with a hard look at designs of clinical investigation of antianginal drugs. The difficulties in carrying out an ideal antianginal drug study were highlighted.

Silent myocardial ischemia, a subject currently of great concern and interest, was discussed by Dr. Andrew Selwyn. Dr. William Shell followed with a preliminary study demonstrating the potential utility of transcutaneous nitroglycerin patches for silent ischemia. Dr. John Parker then addressed the problem of

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nitrate attenuation or "tolerance," specifically analyzing sustained-release nitroglycerin preparations. Dr. John Flaherty proposed alternative dosing strategies for the transcutaneous patches as a potential means of avoiding tolerance.

Now in its second century of clinical use, nitroglycerin is a mainstay of antianginal therapy. Innovative delivery systems have certainly extended the use of nitroglycerin beyond the acute painful attack. We are still attempting to learn definitively how the drug improves angina on the hemodynamic and cellular levels, and how it can be used most beneficially in all of its dosage forms. A unique multicenter trial with nitroglycerin patches is now in progress in conjunction with the Food and Drug Administration, the academic community and industry. This study will hopefully provide us with the necessary information on which to base clinical decision-making for the full range of angina patients. We look forward to the results of this trial so that we can determine the most effective use of the transcutaneous patches for the management of angina pectoris in years to come.

Update on Transdermal Nitroglycerin: An Overview

STEPHEN SCHEIDT, MD

Nitroglycerin (NTG) and its congeners have been used for the therapy of angina pectoris for over 100 years.[1] Sublingual administration provides rapid absorption, immediate therapeutic blood levels and rapid relief of acute anginal attacks, with a total duration of action of 15 to 30 minutes. For more prolonged action, organic nitrate esters, including isosorbide dinitrate, pentaerythrityl tetranitrate and others, were designed to overcome the extensive enterohepatic clearance of NTG. Indeed, such drugs can provide hemodynamic and clinical actions of nitrates for several hours. However, there is wide interindividual variability in absorption and metabolism, and such agents must often be administered 4 to 6 times a day.

Another approach to prolonging nitrate action has been alternative delivery systems for NTG itself. This includes oral time-release capsules that release NTG slowly into the gastrointestinal tract, lozenges that are placed in a buccal pouch and absorbed slowly through the mucous membrane of the cheek as the lozenge dissolves[2] and transdermal NTG delivery. NTG ointment has been available since 1955 but has been used widely following a report by Reichek et al[3] in 1974. Absorption of NTG through the skin or mucous membranes, of course, provides direct venous access, bypassing the gastrointestinal tract and the enterohepatic circulation. However, the ointment produces variable plasma levels, depending on the area of application,[4] and is clinically effective for only 3 to 5 hours.[3] Further, it is sometimes messy and inconvenient to apply.

In late 1981, 3 transdermal NTG delivery systems were marketed: Nitro-Dur® (Key Pharmaceuticals), Nitrodisc® (Searle Pharmaceuticals) and Transderm-Nitro® (Ciba Pharmaceuticals). Transdermal patches release NTG at a constant rate over at least 24 hours. The rate of drug release is determined solely by the area of the patch, following 0-order kinetics. Drug delivery is largely unaffected by skin characteristics, patch location or other physiologic characteristics of the patient, rather than being regulated by the device itself.[5] NTG plasma levels are dose dependent, and steady-state plasma levels are reached within 2 hours and maintained for at least 24 hours.[5] NTG plasma levels achieved with transdermal patches have been reported to range from 0.1 to 0.4 ng/ml for patch sizes between 2.5 and 20 mg/24 hours.[6,7] This may be below the lower limit of the therapeutic range for plasma NTG, which is generally accepted as approximately 1.0 ng/ml.[8] However, the method of measuring NTG plasma levels is controversial. Assays are difficult to perform, improper sample handling may lead to loss of the volatile drug and there is disagreement about the value of measuring venous plasma levels, because the sampling site is downstream from most areas of NTG uptake. Although some investigators have suggested that measurement of arterial NTG levels would be much more valuable, few reports are available.

Although transdermal NTG patches have been widely accepted, their use has stimulated much controversy. Several recent editorials[9,10] have noted the dearth of large well-controlled studies proving efficacy of these systems, and much work must be done before firm conclusions can be drawn. However, a surprisingly large number of studies have been performed, albeit with relatively small numbers of patients; results are summarized in Tables I and II.

One group of trials may be termed "short term"; they generally involve monitoring of clinical and hemodynamic variables for up to 24 hours after application of transdermal NTG. Reichek et al[11] studied low- and high-dose transdermal NTG; the low dose was determined by titration to achieve a decrease in systolic blood pressure of at least 10 mm Hg or an increase in heart beat of at least 10 beats/min, and the high dose was the maximum tolerated by the patient, short of incapacitating headache or other major side effects. The mean low dose was 9.4 mg and the mean high dose 24 mg (Nitrodisc) or 22 mg (Transderm-Nitro). At 4 hours after patch application, bicycle exercise time increased 7% with low-dose transdermal NTG, and 29 and 39% with high-dose Nitrodisc and Transderm-Nitro therapy, respectively, although none of these increases achieved statistical significance. At 24 hours, the effects were small and not statistically significant.

Parker et al[12] studied Nitro-Dur in doses of 5, 10, 15, 30 and 45 mg/hour. At 4 hours after patch application,

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TABLE I Short-Term (less than 1 day) Clinical Trials of Transdermal Nitroglycerin for Angina

First Author	Preparation	(Dose) (mg/24 hr)	Other Therapy	Pts. (n)	Exercise Time Increase vs Placebo	
					Early (4 hr)	Late (24 hr)
Reichek[11]	Nitrodisc	9.4 mean[a]	Yes	7	7%	−4%
	Nitrodisc	24 mean[b]		8	29%	5%
	Transderm-Nitro	22 mean[b]		5	39%	0
Parker[12]	Nitro-Dur	5	1/11	11	9%†	6%
		10		11	9%†	4%
		15		11	6%†	−2%
		30		6	35%†	3%
		45		6	31%	6%*
Hollenberg[13]	Nitro-Dur	2.5	?	10	2%	
		5		10	2%	
		10		10	6%	
Naafs[14]	Transderm-Nitro	5	No	10	16%[c]*	
Cerri[15]	Transderm-Nitro	5	No	20	28%[d]*	20%
		10		20	30%[d]*	15%
Pucci[16]	Nitro-Dur	10	2/10	10	63%[d,e]*	45%[e,f]*

* $p < 0.01$; † $p < 0.05$.
[a] Dose titrated to increase heart rate ≥ 10 beats/min or decrease systolic blood pressure ≥ 10 mm Hg.
[b] Maximal tolerated dose short of incapacitating headache or other severe side effects.
[c] Studied at 12 to 16 hours after patch application.
[d] Studied at 3 hours after patch application.
[e] Total work performed.
[f] Studied at 21 hours after patch application.

treadmill exercise duration was significantly prolonged for most doses. However, only the largest dose, 45 mg, prolonged exercise at 24 hours, and this 6% increase, although statistically significant, appears biologically of minor importance.

Hollenberg et al[13] studied 2.5, 5 and 10 mg of Nitro-Dur at 4 and 7 hours after patch application. Although total exercise time changed little, a computerized ST-segment analysis, termed the "treadmill exercise score," was reported to improve by 30% compared with placebo for all transdermal doses studied; 0.6 mg of sublingual NTG showed an even greater improvement in the treadmill exercise score.

Naafs et al[14] reported a 16% prolongation of treadmill exercise compared with placebo, as well as a delay in development of angina during exercise, evaluated 12 to 16 hours after patch application.

Cerri et al[15] found significant improvements of 28 and 30% in exercise time 3 hours after administration of 5 and 10 mg of Transderm-Nitro, respectively, in a nonrandomized crossover study; at 24 hours, improvement in bicycle exercise time was 20 and 15% over placebo for the 5- and 10-mg doses, respectively, but statistical significance was no longer achieved.

Finally, in a nonrandomized, nonblinded study, Pucci et al[16] compared Nitro-Dur, 10 mg/24 hours, to isosorbide dinitrate, 20 mg 3 times a day. Reporting total work performed on a bicycle rather than exercise duration, transdermal NTG produced a 63% increase in total work at 3 hours compared with placebo and a 45% increase at 24 hours, with similar benefit for isosorbide dinitrate.

To summarize, these short-term trials show increase in exercise time compared with placebo at 4 hours after patch administration for both small- and large-dose transdermal NTG. At 24 hours after transdermal NTG administration, benefit is more difficult to show.

Long-Term Studies

In long-term drug trials, a constant dose of transdermal NTG is administered for 1 week or longer, and stress testing is done after administration of the final NTG patch. Parker and Fung[12] found no improvement in exercise time, either at 4 or 24 hours after Nitro-Dur, 15 mg, after 2 weeks of chronic therapy. Hollenberg and Go[13] reported a 25% increase in time to 1 mm of ST-segment depression in 5 patients given Nitro-Dur, 5 mg/day for 4 weeks. Crean et al[17] administered Transderm-Nitro, 5 mg/day to 11 patients for two 2-week crossover periods, and reported a 5% increase in exercise time compared with placebo for the first 2-week period, but a 17% decrease for the third and fourth weeks. Using the maximal tolerated dose of Transderm-Nitro, 10 to 20 mg, they found a 21% increase in total exercise time compared with placebo (difference not significant).

Thompson[18] reported a 30% increase in exercise time at 4 hours and a 25% increase at 26 hours (both $p < 0.01$) after administration of the maximal tolerated dose of Nitrodisc, between 10 and 20 mg, varying according to individual patients.

Martines[19] administered Transderm-Nitro, 5 and 10 mg, for 3 weeks and found a 33% increase in exercise time for the smaller and a 59% increase for the larger dose (both $p < 0.01$), when measured 3 hours after the last transdermal NTG application.

Imhof et al[20] compared Transderm-Nitro, 5 mg, with isosorbide dinitrate, 40 mg 2 times a day, and measured exercise tolerance 3 to 4 hours after the last patch of 2 weeks of therapy. Transdermal NTG significantly prolonged exercise time by 36% compared with baseline measurement ($p < 0.01$); there was also a minor and insignificant improvement compared with isosorbide dinitrate.

Wester and Mouselimis[21] compared Transderm-Nitro, 5 mg, with nifedipine, 20 mg 2 times a day, in an

TABLE II Long-Term Clinical Trials of Transdermal Nitroglycerin (TD-NTG) for Angina

First Author	Preparation	Dose (mg/24 hr)	Duration	Pts. (n)	TD-NTG Exercise Time Increase vs Placebo (P) Early (4 hr)[a]	Late (24 hr)[a]	Anginal Episodes (n/week) P	TD-NTG	Sublingual NTG (tablet/week) P	TD-NTG	Other Results
Parker[12]	Nitro-Dur	15	2 weeks	11	−5%	7%					Sublingual NTG 5 hr after TD-NTG increased exercise time 23% vs TD-NTG
Hollenberg[13]	Nitro-Dur	5	4 weeks	5							25% increased time to 1-mm ST depression
Crean[17]	Transderm	5	1 week	11	5% (wks 1–2) −17% (wks 3–4)		9	10 (+11%)	14	13 (−7%)	35% fewer minutes, 7% fewer episodes ST depression per 96 hours continuous monitoring (both NS)
	Transderm	10–20[b]	1 week	9	21%						
Thompson[18]	Nitrodisc	10–20[b]	10 days	8	30%†	25%†[c]			32	12 (−63%)	
Martines[19]	Transderm	5	3 weeks	24	33%[d]*		7.7	2.6 (−66%)*	8.2	3.2 (−61%)*	51% increase in total work*
		10	3 weeks	24	59%[d]*			0.7 (−91%)*		0.8 (−90%)*	98% increase in total work*
Imhof[20]	Transderm	5	2 weeks	10	36%*		19	4.3 (−78%)*	19	3.9 (−80%)*	Exercise time increased 34% with isosorbide, 40 mg*
Wester[21]	Transderm	5	2 weeks	12	23%[e]*		4.2	2.1 (−50%)*	3.2	1.6 (−50%)*	Exercise time increased 23% with nifedipine, 20 mg*
Sullivan[22]	Transderm	10	3 days	16	0	−4.5%	No consistent pattern				
Georgopoulos[23]	Transderm	5	1–2 weeks	13			10.8	4.0 (−63%)		(−67%)	Sum of all ST depressions with exercise reduced 51% by TD-NTG compared to P
Eberhart	Transderm	5	1 week	12		13%[f]					25% increase in total work*
Yasky	Transderm	20	1 week	16		68%[f]					89% increase in total work*; 126% increased time to 1-mm ST depression
Andreoli	Transderm	5	3 weeks	28		35%*	7.4	3.3 (−55%)*	7.2	4.1 (−57%)*	68% increase in total work*
	Transderm	10	3 weeks	28		65%*		1.4 (−82%)*		1.0 (−86%)*	129% increase in total work*
Kapoor	Transderm	5	2 weeks	30		35%[g]*	10	4 (−60%)*	9	3 (−67%)*	

* $p < 0.01$; † $p < 0.05$.
[a] Time after application of final patch of chronic dosing interval.
[b] Maximal tolerated dose (Table I).
[c] Studied at 26 hours after last patch application.
[d] Studied at 3 hours after last patch application.
[e] Studied at 2 hours after last patch application.
[f] Not analyzed for statistical significance.
[g] Studied at 48 hours after last patch application.
NS = not significant.

open crossover experiment. After 2 weeks of continuous therapy, duration of bicycle exercise, performed 2 hours after patch application, increased 23% with Transderm-Nitro compared with baseline ($p < 0.01$). Nifedipine showed similar benefit.

Sullivan et al[22] administered Transderm-Nitro, 10 mg, in a study intermediate between "short" and "long term," using a 3-day lead-in period. There was no difference in exercise time 1 hour after transdermal NTG or placebo and a 4.5% decrease in peak exerci time with NTG compared with placebo at 24 hou (difference not significant).

Georgopoulos et al[23] administered Transderm-N tro, 5 mg, for 1 to 2 weeks. Exercise duration was n measured, but ST-segment depression at matche treadmill times was reported to be improved 51% b transdermal NTG at 2, 8 and 24 hours after patc application.

Finally, 4 as yet unpublished trials used Transderm-Nitro in varying doses. Eberhardt* and Yasky* administered Transderm-Nitro, 5 mg and 20 mg, respectively, for 1 week in 12 and 16 patients in double-blind, placebo-controlled, crossover protocols. Twenty-four hours after application of the last patch, Eberhardt found a 25% increase in total work and Yasky demonstrated an 89% increase in total work, both reported as statistically significant. Exercise time was increased by 13 and 68%, respectively, but this parameter was not included in analysis for statistical significance. Andreoli* gave Transderm-Nitro 5 and 10 mg for 3 weeks to 28 patients in a double-blind, crossover trial. Twenty-four hours after application of the last patch, exercise time was prolonged 35% for the 5-mg dosage and 65% for the 10-mg dosage (both $p < 0.01$). Kapoor* administered Transderm-Nitro, 5 mg, for 2 weeks in a double-blind, placebo-controlled, crossover trial in 30 patients. Exercise duration increased 35% 48 hours after application of the last patch ($p < 0.01$).

Thus, results of the long-term trials are mixed, with several published studies showing statistically significant increases in exercise time within 2 to 4 hours after application of the last patch,[18–21] whereas only 1 published study[18] revealed a statistically significant increase in exercise time 24 hours or more after application of the last patch. On the other hand, many trials found improvement in parameters other than the stringent one of total exercise time. Indeed, of the 13 trials listed in Table II, 4 showed statistically significant improvement in exercise time at 2 to 4 hours,[18–21] 2 showed improvement at 24 to 26 hours (Thompson[18] and Andreoli*), 1 showed improvement at 48 hours (Kapoor*) and 2 additional trials reported total work rather than exercise time, and this was significantly improved at 24 hours (Eberhardt and Yasky*). In 1 study exercise times were not reported[23] and in only 4[12,13,17,22] were the results completely negative. Even among these 4 negative trials, one showed 25% increased time to 1 mm of ST-segment depression,[13] and another[17] showed 35% fewer minutes and 7% fewer episodes of ST-segment depression in 96 hours of continuous Holter monitoring, although these did not attain statistical significance.

There are a number of reasons for the inconsistencies in data. Study design varies considerably. Some studies were randomized, some were placebo controlled or crossover, and some, but not all, were double blind. Further, even if study design was blinded, it is unclear how successful the blinding was, because NTG tends to be distinguishable from placebo both to the patient, because of such symptoms as headache, and to physicians, because of decreases in blood pressure or increases in heart rate. Some studies allowed other antianginal therapy and some did not. In several studies it is impossible to determine whether or not other therapy was administered concomitantly. The Methods section of many published studies is not sufficiently detailed to determine the relative severity of coronary artery disease. In most cases, coronary angiograms were not required, and anatomic disease in some groups of study patients may have been considerably more severe than in others.

A cause of considerable concern is the frequent reliance on patients who have participated in previous trials of antianginal drugs. The whole question of "training effects" with repeated exercise testing is not addressed or sufficiently detailed in most published studies.

The number of patients was exceedingly small in all of these trials, averaging 10 in the trials of acute therapy (range 5 to 20) and 14.6 in the trials of chronic therapy (range 5 to 28). In many cases, results were reported that would appear to have clinical significance, yet statistical significance was not achieved. This is perhaps most striking in the oft-cited "negative" studies of Reichek et al,[3] in which 29 and 39% increases in exercise time did not achieve statistical significance, perhaps because only 8 and 5 patients were studied with maximal tolerated doses of Nitrodisc and Transderm-Nitro, respectively.

The final and perhaps most difficult issue to address is the question of what measure of efficacy is clinically most relevant. Because of its widespread availability, possible correlation with prognosis and ease of objective comparison, maximal stress testing is often used, and total exercise time is widely regarded as perhaps the most important measurement of efficacy of any antianginal agent. However, exercise to the point of pain is an unusual situation for the average angina patient in daily life. For most physicians, prevention of anginal episodes or increase in the amount of exercise that can be done short of angina, is the general goal of therapy. Five of the long-term trials summarized in Table II did indeed reveal significant reductions in number of anginal episodes or sublingual NTG consumption, or both, with a median reduction of 63% in anginal episodes and 67% in NTG consumption, although such results are generally discounted as too subjective.

Electrocardiographic ST-segment changes in patients with angina will be discussed under the rubric of "silent ischemia" elsewhere in this symposium. If such electrocardiographic changes do indeed represent ischemia, they may provide objective means of quantifying the antiischemic effect of NTG or any other drug on daily activities short of those producing pain. Unfortunately, the data are too sparse in published transdermal NTG trials to permit even the most tentative of conclusions concerning this therapeutic endpoint.

Given the small number of trials, the differences in study design, the frequent lack of individualized or titrated dosage of transdermal nitroglycerin, the small numbers of patients in most trials, the differences in patient selection and the reliance on only a single objective measurement of efficacy, the exercise stress test, it is not surprising that no clear answer is available concerning the efficacy of transdermal NTG. The final conclusion probably will not be either so enthusiastically favorable as greeted the transdermal NTG patches when first released or so unfavorable as recent

* Personal communication, H. Rosenbach, CIBA Medical Affairs, Summit, New Jersey.

reviews have suggested. Until more research is reported, physicians must recognize that there will be variability in responses of individual patients, as well as in doses of transdermal NTG needed to achieve the optimal response.

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Pharmacology of the Nitrates in Angina Pectoris

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Nitrate therapy is the oldest treatment modality for angina pectoris. In addition to sublingual nitroglycerin, longer-acting preparations are available to provide angina prophylaxis. Nitrates work as venodilators and arterial dilators, and by these actions in patients with angina pectoris can reduce myocardial oxygen demands while maintaining or increasing coronary artery flow. On the cellular level, they may increase endothelial prostacyclin release to cause their vasodilating effects. Long-acting nitrates are available in sublingual, chewable, oral, buccal and topical forms. The topical forms include nitroglycerin paste and transcutaneous patches. Long-acting nitrates have a duration of action of 2 to 24 hours, depending on the preparation used. The transcutaneous patches, which provide the longest duration of activity, are being reexamined regarding long-term efficacy and drug tolerance. Nitrates are also available in an intravenous form and in a short-acting sublingual spray soon to be released. The safety of nitrates has been confirmed. Their hemodynamic and safety profiles allow them to be combined with calcium-channel blockers, β-adrenergic blockers or both when trying to improve on the antianginal efficacy of single-drug therapy.

(Am J Cardiol 1985;56:8I–13I)

Organic nitrates are the oldest and most frequently used medications for the urgent treatment of angina pectoris. Nitroglycerin (NTG) was first synthesized by Sobrero in 1846, and he observed that a small quantity of the oily substance placed under the tongue elicited a severe headache. In 1847, Hering developed the sublingual dosage form of NTG, which he advocated for treatment of a number of diseases. In 1857, Brunton administered amyl nitrite, a known vasodepressor, by inhalation and noted that anginal pain was relieved within 30 to 60 seconds. The action of amyl nitrite was transient, however, and the dosage was difficult to adjust. In 1879, Murrell decided that the action of NTG was similar to that of amyl nitrite and used sublingual NTG for the relief of acute anginal attacks and as a prophylactic agent to be taken before exercise. In 1939, Krantz et al[1] reported on their discovery of isosorbide dinitrate. The observations that organic nitrates could be used safely for the rapid and long-term alleviation of angina pectoris led to the widespread acceptance of these compounds.

Chemistry

Organic nitrates are polyol esters of nitric acid, whereas organic nitrites are esters of nitrous acid. Nitrate esters (C-O-NO_3) and nitrite esters (C-O-NO_2) are characterized by a sequence of carbon, oxygen and nitrogen, whereas nitro compounds (which are not vasodilators) possess carbon-nitrogen bonds (C-NO_2). Thus, glyceryl trinitrate (commonly called nitro) is not a nitro compound and is erroneously called nitroglycerin. However, this nomenclature is in widespread use and will be used throughout this review.

Amyl nitrite is a highly volatile liquid that is administered by inhalation. Organic nitrates of low molecular weight, such as NTG, are moderately volatile, oily liquids, whereas high-molecular-weight nitrate esters, such as erythrityl tetranitrate and isosorbide dinitrate (ISDN), are solids. The fully nitrated polyols are partially soluble, and incompletely nitrated compounds are more soluble in water.[2]

Hemodynamic Effects

NTG and organic nitrates are direct dilators of arteries and veins (Table I).[3] The drugs have no direct effects on the myocardium or the cardiac conduction system. Nitrates are taken up directly by blood vessels, which, along with the liver, are involved with metabolic degradation of the drugs.[4]

Nitrates in low plasma concentrations dilate the veins.[5] Maximal venodilation is observed with small to moderate doses of nitrates. Arterial vasodilation becomes more pronounced at higher plasma and tissue nitrate concentrations. With even higher nitrate concentrations, dilation of the systemic and coronary arteriolar circulations occur, with a reduction in both peripheral and coronary vascular resistances.

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The magnitude of the vascular response to short-term administration of nitrates parallels the administered dose. However, with long-term administration, the dose-response relation is not seen, probably secondary to nitrate metabolite accumulation.[6] Whether the responsiveness of various regional circulations differ in response to nitrates is not known.

Cellular Mechanisms of Nitrate Action

Nitrates are believed to induce vasodilation by interacting with sulfhydryl groups on nitrate receptors on cell membranes.[7] Nitrates also combine with sulfhydryls within smooth muscles, where they are converted to S-nitrosothiols. These are short-lived compounds that induce an increase in cyclic guanosine monophosphate production, which triggers vasodilation.[8]

Recent studies suggest that the prostaglandins may play a role in NTG-induced vasodilation.[9,10] In open-chest dogs, NTG caused a significant increase in coronary sinus prostaglandin E concentration, which correlated with an increase in heart rate, a decrease in mean arterial blood pressure, an increase in mean coronary artery blood flow and a decrease in mean coronary resistance. After administration of indomethacin (5 mg/kg), trinitroglycerin infusion produced a significantly smaller decrease in coronary vascular resistance and systemic blood pressure and no increase in coronary sinus prostaglandin E concentration.[9] Based on these results, Morcillio et al[9] concluded that the mechanism of action of trinitroglycerin on coronary and systemic resistance may be mediated, at least in part, through the prostaglandin system. Levin et al[10] reported that NTG stimulates synthesis of prostacyclin, a potent coronary and systemic vasodilator, by cultured chick embryo endothelial cells. An increase in NTG concentration produces a dose-related increase in the concentration of 6-keto-$PGF_{1\alpha}$ (Fig. 1).[10] This increase in prostacyclin release from endothelial cells with increasing nitrate doses, and the inhibition of thromboxane (TXB_2) by platelets, further support the concept that prostaglandins may play an important role in the vasodilatation caused by nitrates.

Mechanisms of Angina Relief with Nitrates

It is not exactly known how nitrates relieve angina pectoris.[11] Multiple antiischemic mechanisms may be involved (Fig. 2)[11–13] and the drugs appear to affect favorably both the myocardial oxygen demand and supply.

In the peripheral circulation, nitrates reduce both arterial vascular resistance and venous tone. Accordingly, a reduction in systolic arterial pressure and a decrease in venous pressure, with a resultant decrease in ventricular volume, reduces the ventricular wall tension that is required to generate a given pressure in accordance with the Laplace relation. Taken together with a modest decrease in arterial pressure, these changes result in a reduction in myocardial oxygen demands.[13]

NTG can also increase coronary blood flow and oxygen supply by reducing coronary arterial spasm that may occur at fixed stenotic sites in the coronary vasculature. In addition, dilation of coronary collaterals occurs, whereas autoregulation in the normal vascular bed persists so that a coronary "steal" does not ensue. To the degree by which diastolic ventricular filling pressure is reduced by nitrates, while arterial pressure is not lowered significantly, there is an improvement in the perfusion gradient for coronary flow to occur, which may be very beneficial, especially in the presence of left ventricular failure.[13]

Thus, ischemia is relieved by nitrates from both a decrease in myocardial requirements and an increase in oxygen supply. In any particular patient, any one or all of these hemodynamic benefits may occur, with improvement of the ischemic state. For this reason,

TABLE I Effects of Nitrates

Marked venodilation
Decreased right and left atrial pressures
Decreased stroke volume
Decreased arterial pressure
Reflex tachycardia
Slight arteriolar dilation
Decreased arterial pressure
Increased stroke volume
Dilation of epicardial coronary arteries
Dilation of collaterals

Reproduced with permission from Cardiovasc Rev Rep.[3]

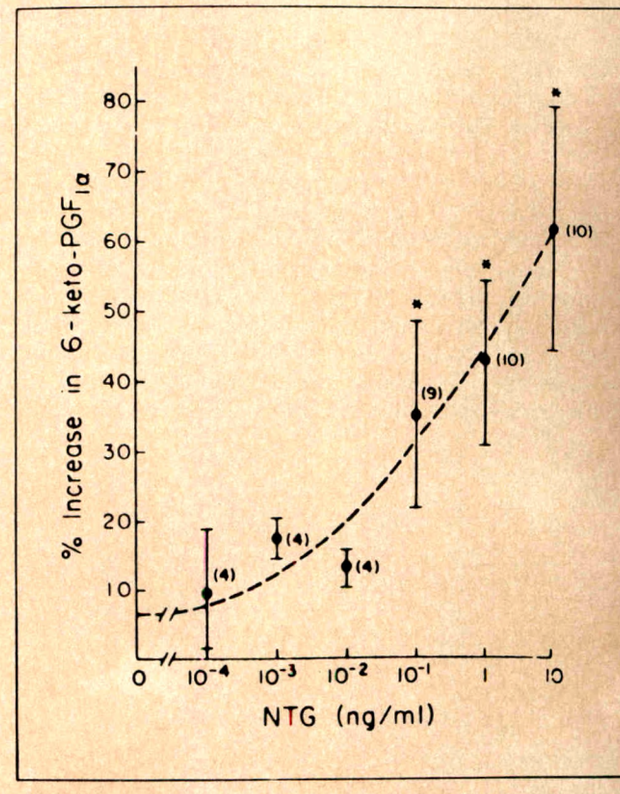

FIGURE 1. Nitroglycerin (NTG) causes a dose-related increase in 6-keto-$PGF_{1\alpha}$, a stable hydrolysis product of prostacyclin in cultured endothelial cells. The release of prostacyclin and the inhibition of thromboxane (TXB_2) may in part mediate the vasodilatation caused by the nitrates. Reproduced with permission from J Clin Invest.[10]

TABLE II Hemodynamic Effects of Nitrates, Beta Blockers and Combination Treatment

	Nitrates	Beta Blockers	Combination
Heart rate	↑ (reflex)	↓	↓ ↔
Contractility	↑ (reflex)	↓	↔
Wall tension	↓	↔	↓
Systemic blood pressure	↓	↓	↓
Left ventricular volume	↓	↑	↔ ↑
Coronary resistance	↓	↑ ↔	↓ ↔

Reproduced with permission from McGraw-Hill.[14]

TABLE III Hemodynamic Rationale for Combining Nitrates and Calcium-Entry Blockers in Angina Pectoris

	Nitrates	Calcium Blockers	Combination
Heart rate	↑ (reflex)	±	↑ (reflex)
Blood pressure	↓	↓	↓↓
Heart size	↓ / 0	± / ↑	0
Contractility	↑ (reflex)	↓	0
Venomotor tone	↓	0	↓
Peripheral resistance	↓	↓	↓↓ ?
Coronary resistance	↓	↓	↓↓ ?
Coronary blood flow	↑	↑	↑↑ ?
Collateral blood flow	↑	↑	↑↑ ?

Reproduced with permission from McGraw-Hill.[15]
± = questionable additive effects; ↓ = decrease; 0 = no change; ↑ = increase.

nitrates remain a primary treatment for patients with angina pectoris.

The hemodynamic actions of nitrates allow them to be combined with other antianginal drug groups—β-adrenergic blockers and calcium-channel blockers. The hemodynamic effects of these combinations (Tables II and III) may provide increased antianginal efficacy over single drug use.[14,15]

General Principles of Therapy

Sublingual administration of NTG has long-standing universal acceptance as antianginal therapy. Because of its brief duration of action, many attempts have been made to prolong the drug's therapeutic effect by altering molecular configuration or route of administration. Currently available preparations are NTG (sublingual tablet or spray), sustained-release formulations of NTG, NTG ointment and a number of synthetic nitrate esters (ISDN, erythrityl tetranitrate and pentaerythrityl tetranitrate). In addition to the sublingual, topical and oral routes of administration, intravenous, long-acting transdermal and long-acting transmucosal NTG preparations have recently become available. As a result, an era of effective NTG prophylaxis has begun. To provide optimal benefit to patients, clinicians must use NTG more systematically and critically than in the past. Several basic considerations remain central in effective NTG use. When acute relief of established ischemia is the goal, rapid onset of effect is essential, and duration of effect is less important. In contrast, for prevention of angina, predictability and duration of effect are the central issues. Moreover, individual patients may show marked variability in the dose needed to obtain a given effect. Because optimal dosage is unpredictable, careful titration for each patient is needed. A dose producing orthostatic changes in heart rate at rest of 10 beats/min and systolic blood pressure of 10 mm Hg is a practical guide. Such a dose of any nitrate preparation will have antianginal effects, although larger doses may also be tolerated.

Routes of Administration[16,17]

Sublingual: Sublingual NTG avoids first-pass metabolism, so that a transient but effective concentration of drug rapidly appears in the circulation. Relief from acute attacks of angina pectoris begins within 2 to 5 minutes. Its clinical and hemodynamic effects diminish rapidly because of the drug's hepatic breakdown and are usually undetectable by 1 hour. Hence, sublingual administration of NTG (tablet or spray) is most appropriately used for quick relief of acute attacks of angina pectoris. It can also be used for brief periods of anginal prophylaxis in patients with highly predictable angina. When taken immediately before those life-style events likely to provoke an attack, it can prevent onset of symptoms for up to 30 minutes. Otherwise, it is unsuitable for prophylactic use.

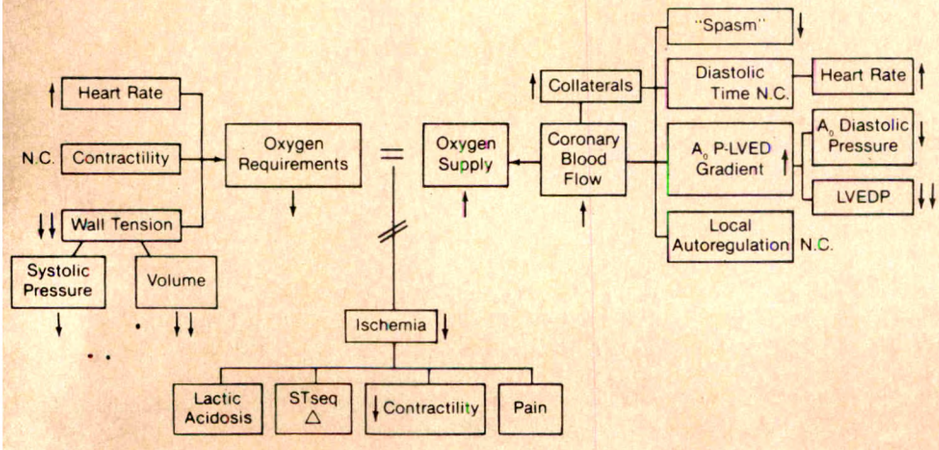

FIGURE 2. Effects of nitrates on the balance between oxygen requirements and supply. Although a reflex increase in heart rate would tend to reduce the time for coronary flow, dilation of collaterals and enhancement of the pressure gradient for flow to occur as the LVEDP falls tends to increase coronary flow. AoP = aortic pressure; LVEDP = left ventricular end-diastolic pressure; NC = no change. Reproduced with permission from Cardiovasc Rev Rep.[13]

Preparations come in tablet, capsule or aerosol form, containing from 0.15 mg to 0.6 mg of NTG (Table IV). If symptoms are not relieved by a single dose, additional doses may be taken at 5-minute intervals, but no more than 3 tablets should be used within a 15-minute period. Because NTG gradually loses potency in the tablet form through volatilization, it is packaged in glass containers with tightly fitting metal screw caps. Tablets should be kept in the original container with the lid tightly closed after each use, and the compound should not be exposed to heat. Physicians should take ample time to explain to patients how to use NTG correctly, because studies indicate that many patients fail to obtain maximal benefit from it, especially as a short-term prophylactic agent.

Sublingual and chewable preparations of ISDN and NTG congeners have been developed to prolong nitrate effectiveness by reducing hepatic deactivation. Unfortunately, they also have a weaker effect on vascular smooth muscle. As a result, these molecular alterations have no inherent superior benefit, because much higher doses are needed to obtain equipotent effects (Table IV). Doses as high as 30 mg have been frequently administered. Onset of action is from 3 to 15 minutes, and effect may last for as long as 2 hours. The prolonged effect would probably not exceed equipotent doses of sublingual NTG. The Food and Drug Administration classifies these drugs as "probably" effective for the treatment of acute anginal attacks and for prophylaxis in those situations likely to evoke such attacks.

Oral administration: Despite controversy regarding their beneficial effect, oral NTG and nitrate esters have found widespread use in the therapy of angina pectoris. Because of extensive first-pass metabolism, large doses (e.g., 30 mg of ISDN 4 times a day) are needed to overwhelm hepatic enzymatic breakdown so that substantial amounts of the active form can reach the systemic circulation. Relative to the other nitrates at equipotent doses, onset of effect is approximately 30 minutes and duration of action only 3 hours after oral ISDN. With larger doses, a longer duration of action is achieved. For all oral preparations, doses often greater than those recommended by manufacturers may be necessary to produce the desired therapeutic effect. Such large doses are likely to cause significant orthostatic effects and severe headaches. With long-term administration, there are signs of partial tolerance; duration and magnitude of effect have been shown to diminish.[18,19] Sustained-release oral preparations are now available and appear to have a longer duration of action (Table IV).

Topical administration: NTG ointment or paste was developed more than 25 years ago, but not until 1974 were its sustained therapeutic effects for up to 3 to 4 hours accepted.[20] Usually a 2% NTG ointment is applied to the skin in 1- to 3-inch doses (15 mg/inch) and then spread in a uniform layer. Because skin permeability increases with increased hydration, covering the applied area with plastic and taping the edges will increase water content of the skin and enhance absorption. It will also prevent the medication from ending up on the patient's gown or clothing. Studies reveal that anterior chest wall or upper limb application derives optimal clinical benefits while keeping headaches to a relative minimum. Absorption may be variable, and the delay in onset of action is approximately 30 minutes.

TABLE IV Dosage and Kinetics of Nitroglycerin and Long-Acting Nitrates

Medication	Usual Dosage	Onset of Action	Duration of Action
Sublingual NTG	0.3–0.6 mg	2–5 min	10–30 min
Aerosol NTG	0.4 mg	2–5 min	10–30 min
Sublingual and chewable ISDN	2.5–10 mg	3–15 min	1–2 h
Sublingual and chewable ET	5–15 mg, 10 mg	3–15 min	2 h
Transmucosal NTG	1–3 mg	2–5 min	3–5 h*
Oral NTG (SR)	2.5–9 mg	30–45 min	2–8 h*
Oral ISDN	5–30 mg	15–30 min	3–6 h
Oral ISDN (SR)	40 mg	30–60 min	6–10 h
Oral ET	10 mg	30 min	Variable
Oral PET	10–40 mg	30 min	3–6 h
Oral PET (SR)	30–80 mg	Slow	6–10 h
Oral ointment (2%)	½–2 inches	20–60 min	3–8 h
Transdermal NTG	5–10 mg	30–60 min	Up to 24 h
Intravenous NTG	5–300 μg/min	Immediate	Transient

* Duration of action lengthens with increasing dosage.
Adapted with permission from Am J Med.[16]
ET = erythrityl tetranitrate; ISDN = isosorbide dinitrate; NTG = nitroglycerin; PET = pentaerythrityl tetranitrate; SR = sustained release.

Cutaneous administration of NTG permits gradual absorption, yielding a truly long-acting effect. Topical application is recommended for the prevention and treatment of anginal attacks, especially at night. The optimal dosage is determined by starting with a half inch of ointment and increasing by half an inch every 3 to 4 hours until headache occurs, then decreasing to the largest dose that does not cause headache. Sites of application should be rotated to avoid skin irritation.[21] Although long-term administration does not clinically appear to lead to tolerance, gradual reduction in dosage and frequency of application over a 4- to 6-week period is advised to prevent withdrawal symptoms during termination of treatment.[20,21]

Recently, 3 slow-release transdermal NTG preparations have been marketed, with the hope of providing a simple once-a-day method for constant antianginal prophylaxis. The preparations contain NTG and a reservoir material and are designed to continuously release NTG into the circulation over 24 hours after a single application. Unfortunately, despite tremendous patient satisfaction with these patches, the clinical data available to date have not shown the long-term clinical efficacy envisioned.[22–24] The relatively small doses used provide 24-hour blood levels equivalent to the levels obtained using half an inch of NTG paste applied every 8 hours. These low reference levels may not provide effective antianginal prophylaxis regardless of route of administration. Additionally, data predicting therapeutic effect from blood levels is lacking for all long-acting nitrates. Until convincing data are available, it may be unwise for physicians to rely solely on any one of these preparations on a once-a-day basis

in patients with rest pain, coronary spasm or in those who are severely limited. Despite these drawbacks, data should be forthcoming from studies using larger doses, indicating that these products will fulfill their promise to provide continuous, long-term antianginal prophylaxis.

Buccal nitroglycerin: Pharmaceutical manufacturers continue to demonstrate considerable creativity in devising new formulations of NTG. The latest release is long-acting transmucosal NTG.[25,26] This product contains NTG in an inert polymer base that releases the NTG over a sustained period. As with sublingual NTG, onset of action is almost immediate, and as with long-acting transdermal preparations, nitrate release is gradual and uniform, lasting for as long as 5 hours. Hence, patients can use buccal NTG for relief of an acute angina attack as well as for long-term prophylaxis.

The tablet may be inserted under the upper lip, between the buccal mucosa and gingiva or in the buccal pouch. Patients can eat, drink and talk while the tablet is present. Another attractive feature is the close correlation between therapeutic effectiveness and physical presence of the tablet in the mouth. As with sublingual NTG, a suitable starting dose may be determined by checking for orthostatic changes at 3 minutes after administration. If angina persists or recurs, it need only be determined whether the attack occurred when the tablet was present or already dissolved. If present, a larger dose may be used. If dissolved, administration should be more frequent. Hence, with the combination of all of these practical features in the buccal form, a single nitrate may be substituted for the multiple drug regimens now commonly used.

Intravenous nitroglycerin: An NTG formulation for intravenous administration is available in the United States. Infusions may be used, with dilutions of 25 to 400 μg/ml; the concentration is based on the patient's fluid requirements. Initial dosage should be 5 μg/min, with increases of 4 μg/min every 3 to 5 minutes until a drop in blood pressure or a decrease in pain is noted. If no response is seen with a dose of 20 μg/min, increments of 10 and, later, 20 μg/min may be used.

There is no fixed optimal dose. Because of variations in the responsiveness of individual patients, each patient must be titrated to his or her desired level of hemodynamic function. Because NTG adsorbs onto plastic, special tubings have been synthesized to overcome this problem. Intravenous NTG is indicated in acutely ill patients who are hospitalized and when another route of administration is not feasible. It is also efficacious in such conditions as complicated myocardial infarction,[27] unstable angina, coronary vasospasm, pulmonary edema and hypertension, and during coronary bypass or neurosurgical procedures. At high concentrations, intravenous NTG is a potent arterial as well as venous dilator.

Noncardiac Effects

Because smooth muscle is generally dilated, gastrointestinal motility, esophageal spasm and biliary tree spasm are decreased. The genitourinary system may be similarly affected. The relief of angina pectoris and esophageal spasm may not be differentiated. Studies indicate that pulmonary vasculature dilates, pulmonary artery pressure decreases and there is mild bronchodilation.[2]

Absorption, Metabolism and Excretion

The biotransformation of organic nitrates is the result of reductive hydrolysis catalyzed by the hepatic enzyme glutathione organic nitrate reductase. The enzyme converts the lipid-soluble organic nitrate esters into more water-soluble denitrated metabolites and inorganic nitrite. The partially and fully denitrated metabolites are considerably less potent vasodilators than are the parent compounds. The liver has the enormous capacity to catalyze this reaction. The biotransformation of organic nitrates is a major factor determining their duration of action and the relative efficacy of the drugs given by different routes of administration.[2]

Tolerance and Dependence

A major concern of long-term nitrate therapy is whether tolerance develops to these drugs. Nitrate tolerance was first documented in animal in vitro studies by Needleman et al[28] on vascular strips. These studies found a tolerance effect that was related to nitrates reacting with reduced sulfhydryl groups on a cell membrane, leading to the formation of disulfide linkages and the release of inorganic nitrite (denitrated metabolites). This reaction is believed to convert the "nitrate receptor" to the disulfide form, which has a lower affinity for the nitrates. In humans, the fact that the vascular headaches occurring after nitrate administration often disappear with continued use of the drugs suggests that some form of tolerance is occurring. Indeed, several investigators have reported tolerance to nitrates in humans.

Despite many published warnings about nitrate tolerance,[29–32] little evidence is available to suggest that it is a common clinical problem. However, some data do indicate decreased antianginal effectiveness with long-term use of large doses administered orally.[29–32] Studies of exercise-induced angina confirm some attenuation of the effects of nitrates on heart rate and systolic blood pressure after long-term therapy.[30] Overall, however, the antianginal benefit provided by long-acting nitrates appears to be persistent, and the efficacy of NTG for the management of an acute anginal attack remains unimpaired.

Because large-dose usage is increasing and there are newer preparations aimed at long-term prophylaxis, clinicians must be cautious of the possible development of withdrawal symptoms. The industrial medical literature is replete with descriptions of withdrawal symptoms, including severe headaches, chest pain, acute myocardial infarction and even sudden death in workers chronically exposed to nitrate powder and vapor.

Until more information is available regarding the long-term effects of large doses of nitrates, the clini-

cian should be cautious regarding continuous nitrate prophylaxis, especially in patients with only mild angina pectoris. Most important, patients should be cautioned not to discontinue nitrate medications abruptly.

Side Effects

In general, nitrates are well tolerated. Headaches and postural dizziness are the most frequent side effects, and are often noted early during treatment. The headaches usually disappear after several days to 2 weeks and may be controlled by temporary reduction in dosage. In some patients, generalized vasodilation may cause profound hypotension. The hypotension and resultant reflex tachycardia can reduce coronary perfusion pressure and worsen anginal symptoms. As a result, all patients should be instructed to be in the supine position when taking an NTG preparation until susceptibility to orthostatic hypertension is determined.

Nitrates sometimes cause mild nausea. Patients with glaucoma can safely use NTG.

Contraindications

Hypersensitivity or an idiosyncratic reaction to nitrates contraindicate their use. Because these drugs may increase intracranial pressure, they should be used with great caution in patients with head trauma, cerebral hemorrhage or postural hypotension. Angina pectoris owing to valvular aortic stenosis or obstructive cardiomyopathy should not be treated with nitrates, as the decrease in preload may seriously decrease cardiac output or precipitate pulmonary edema.

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Problems Associated with Clinical Evaluation of Antianginal Medications

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Assessing the efficacy of antianginal medications is not as easy as it might first appear. Many factors, including the protocol, the subjects chosen for study and the physicians conducting the trial, may produce study bias and thereby yield equivocal results. Objectively attempting to quantitate a subjective event such as angina inherently poses many difficulties. The variable nature of anginal episodes makes identification of attacks, or conversely, elimination of such attacks, difficult to assess.

In terms of the protocol, it is necessary to determine what indexes will be used as criteria of efficacy, what doses, either standard or maximally tolerated, will be used for study and what measures will be taken to nullify placebo effect. In terms of patient selection, the varying methods of confirming the diagnosis of ischemia and the questions of concurrent illness, compliance and life-style alterations are all factors that can make findings difficult to elucidate. Finally, investigator bias may be introduced into study results because of prestudy prejudice, involvement in data acquisition and interpretation of findings. It is unlikely that any investigator or group of investigators will ever produce a protocol applicable to all types of antianginal medications that will be universally convincing. Conclusions regarding the efficacy of any antianginal medication will undoubtedly continue to be predicated on assessments made by independent investigators using a variety of research protocols, none of which is likely to be perfect.

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The typical angina episode, vividly described by Heberden[1] and Osler,[2] respectively, as a "choking" or "strangling" sensation associated with the feeling of "impending doom," would seem unlikely to pass without notice. To determine the clinical efficacy of an antianginal agent, it should then be a simple matter of having subjects who have angina record the number of attacks during a specific time interval and then determine whether the number of attacks is significantly reduced during a similar interval in which they are being treated with an antianginal agent. Unfortunately, this task is nowhere near as easy as it first appears, and numerous investigators have expended enormous amounts of time, energy and resources to determine whether new "antianginal" formulations are truly effective.

The Protocol: What Shall We Measure?

Not all anginal episodes are as distinct as those described by Heberden and Osler. In reality, angina is a subjective sensation of discomfort that is characterized somewhat differently by each patient experiencing it.[3] While the classic presentation of substernal chest pressure afflicts a significant number of patients, others may experience coronary ischemic symptoms such as pain or discomfort in the neck, jaw, shoulder, arm or back. It may also take the form of indigestion, heartburn, nausea or breathlessness.[4] Thus, any ailment that produces any of these types of symptoms can easily be confused with angina, and episodes counted as angina may have little or nothing to do with coronary circulatory problems. Conversely, episodes of true coronary ischemia may easily be overlooked by the patient who misconstrues anginal discomfort, ascribing it to an unrelated malady.

Even in patients with well-defined anginal patterns, degrees of severity are found that range from extremely mild to extremely severe, and in counting attacks, it is not clear whether an attack of mild severity should count to the same degree as an extreme one. Patients often learn to attenuate or terminate the activity that appears to be producing angina, and thus, minor alterations in activity patterns may significantly affect reports of anginal frequency.

The number of anginal attacks can also be altered through the use of prophylactic sublingual nitroglycerin (NTG). When a person is about to perform an

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activity known to produce angina, it is an appropriate and accepted practice to self-administer NTG sublingually in anticipation of increased cardiac work. By this method, angina may to a large degree be prevented. Should the patient be given a long-acting agent that raises the anginal threshold, the prophylactic use of sublingual NTG may be voluntarily reduced, but the difference between treatment and pretreatment anginal attack frequency would be obscured in spite of the effectiveness of the test medication. Thus, it becomes essential in long-term studies to consider the number of prophylactic sublingual NTG in tablets taken by the subjects.

Recent studies using sensitive Holter monitoring techniques have confirmed the presence of intermittent asymptomatic myocardial ischemia.[5,6] It has been demonstrated that patients with overt angina are frequently unaware of many ischemic events that occur throughout the day. Additionally, many who are afflicted with coronary occlusive disease have no awareness of the presence of myocardial ischemia even though electrocardiographic changes that suggest cardiac muscle jeopardy occur frequently. Thus, in considering the efficacy of an antianginal medication, it may be appropriate to monitor ST-segment changes on the electrocardiogram around the clock to include episodes of silent ischemia as well as overt ischemia in the counting of ischemic episodes experienced.

Attempts to avoid the problems that result from the subjective nature of anginal symptoms by measuring serum levels of an agent under investigation have also met with difficulty. Such studies begin with the assumption that a particular substance is effective in the treatment of angina and then attempt to determine whether the agent in question provides "therapeutic" levels of the substance in the serum of the subject being treated. If such levels are achieved, the substance is considered effective; if not, it is considered ineffective. In addition to the difficulties associated with accurately assessing levels of medications that appear in nanogram or picogram quantities,[7] the basic premise—that "therapeutic level equals therapeutic effect"—may not be correct. Gradual attenuation of certain effects (tolerance) has been clearly demonstrated with many pharmacologic agents, such as prazosin and β blockers, and may also be present in nitrates and perhaps in calcium-channel blockers. Thus, the level of medication capable of producing hemodynamic changes at one time may be insufficient to produce similar hemodynamic changes at a later date.[8]

Inability to measure blood levels of antianginal medications accurately led to major damage to the credibility of the pharmaceutical industry as a result of studies reported in the early 1970s. In spite of the widespread use and acceptance of long-acting oral nitrates at that time, inadequacies in experiments with rat livers led to the erroneous but widely publicized conclusion that "orally administered organic nitrates are absorbed in the portal circulation and are rapidly and completely degraded by liver enzymes before reaching the systemic circulation and therefore can have little chance of producing vasodilation."[9] Such reports led W. S. Aronow and others to conclude that "long-acting nitrates are ineffective as antianginal agents."[9–11] As a result, there was a significant reduction in the use of long-acting oral nitrates until subsequent work confirmed the presence not only of active agent in posthepatic blood but also of biologically active metabolites.[12] Additional clinical investigation by Aronow[13] led to the conclusion that the data accumulated from the initial rat studies "no longer appear relevant to considerations regarding patients." On the positive side of this controversy, it must be said that the initial skepticism did in fact lead to additional investigation, which further clarified the physiology, pharmacology and dose-response relations of orally administered nitrates.

The difficulties encountered with assessing changes in frequency of angina, use of sublingual nitroglycerin and serum levels have led the Food and Drug Administration to develop criteria for assessing the efficacy of antianginal agents based primarily on symptom-limited treadmill exercise testing.[14] This method assumes that a patient's anginal threshold can be accurately and reproducibly quantitated and that an agent's effectiveness can be determined by comparing pretreatment performance with performance during therapy.

Unfortunately, the significant day-to-day variation in a subject's treadmill performance[15] and the circadian changes in exercise capacity make this method less than ideal.[16] There is, in addition, a "training" effect associated with repetitive exercise testing, related not to actual physical conditioning but rather to learning the treadmill walking technique.[17] These fluctuations in exercise performance led to the acceptance of a ±15% variation in treadmill time as a tolerable baseline value for determining pretreatment capacity. This variation, however, might completely obscure a positive response to active agent in studies not using enough qualified patients.

Subject fatigue, an additional problem associated with exercise testing that has been encountered in the evaluation of the long-acting transdermal NTG preparations, may be important. Because these patches are thought to be effective for 24 hours or more, many studies designed to assess them require patients with presumed ischemic heart disease—relatively deconditioned subjects—to exercise to the point of maximal tolerable angina as many as 5 times in the same day.[18] This can average as much as 35 minutes of exercise for patients who are generally accustomed to only limited activity. These same patients are then asked to return early the next morning for yet another exercise test to determine if the patch has maintained efficacy 24 hours after application. The role of muscle fatigue and musculoskeletal pain in limiting a subject's performance at that time needs to be evaluated before results of such studies can be convincing.

Secondly, and more fundamentally, it is not clear whether maximal exercise testing is appropriate for the evaluation of these long-acting preparations, because the 2 most important determinants of treadmill performance, heart rate and blood pressure, are not significantly affected by nitrates at high levels of exer-

cise.[19] Thus, the coronary vasodilatory component of nitrate activity and its role in prevention of coronary vasospasm at lower levels of activity are overlooked by studies predicated solely on exercise performance.[20–22]

Nullifying the Placebo Effect

A major consideration in the design of any clinical research is the placebo effect. It is well established that significant untoward reactions, as well as major improvement in symptoms, can be produced by the administration of placebo. Failure to consider the extent to which adverse effects occur as a result of a placebo may result in the underestimation of the utility of a medication. At the same time, failure to consider a placebo's positive effects may also lead to overestimation of positive response, since many individuals indicate subjective improvement in symptoms and actually perform better in objective tests after administration of an inert substance. Because angina is a subjective sensation, it is not surprising that the effect of placebo on persons with angina may be quite profound. Thus, it is necessary to begin with a research design that includes accurate determination of a clinical baseline value and then compares the response of a group of subjects receiving placebo with their response to active agent. Additional credibility is gained by then proceeding to a washout phase followed by crossover to allow for group comparisons as well as individual comparisons.

Establishment of accurate baseline values is made difficult for a number of reasons. Accurate record-keeping by the study participants is difficult and often unreliable. Climatic variations, which occur during a prolonged study, may be significant, because subjects with a component of coronary vasospasm may develop more attacks during the cold winter months than during the warm months. In addition, patients or their physicians may alter other antianginal medications during the study, a factor that affects not only the baseline but also affects subsequent portions of the research.

Several recent works indicate that various combinations of antianginal medications may be more effective than others.[23,24] It has been suggested that the combination of nitrates with β blockers may be more effective in the treatment of angina than the combination of nitrates with calcium-channel blockers. In addition, the use of members of all 3 categories of antianginal agents (nitrates, β blockers and calcium-channel blockers) may, in many persons, be less effective than the use of any 2 of these agents.[25] Thus, it may be inappropriate to test the efficacy of antianginal medications without discontinuing all other long-acting antianginal agents during the test. Some of the recent work assessing efficacy of the transdermal NTG preparations studied patients in whom nitrates were added to calcium-channel blockers or β blockers in an uncontrolled fashion.[26] Thus, data from these studies must be discounted, owing to the unpredictability and variability of interaction between these groups of medications.

There are also problems with keeping clinical trials "blind" throughout their course, particularly when the agent being tested is obviously effective. When the patients become aware of the salutary effect of the medication, their reports of efficacy and adverse effects can no longer be considered unbiased. Conversely, when uncomfortable adverse effects develop, patient responses to objective testing may be significantly attenuated. In testing transdermal NTG preparations, in which the delivery system is visible to the patient, subjective response to the esthetics of the patch may also play a role in subjective as well as objective response.[27] It is also difficult to produce a double-blind study when investigators are allowed to measure physiologic parameters such as blood pressure and heart rate. In many cases, comparison with baseline data easily allows for the identification of patients receiving active agent. This knowledge may prevent the unbiased acquisition of objective and subjective data.

The Patient: Whom Shall We Test?

Identification of patients with chronic stable angina pectoris produced by coronary occlusive disease who have no contraindications to participation in research protocol and who are willing to do so is a difficult and time-consuming task. On the basis of history alone, the diagnosis of coronary occlusive disease may be made with a reasonable degree of accuracy. This degree of accuracy, however, may not be sufficient to provide meaningful data in the study of antianginal medications, where placebo effects may be profound and the differences between treatment group and placebo group may be small. It is therefore necessary to confirm the diagnosis using one of several criteria. A positive exercise test based on changes in the ST segment of the electrocardiogram is of little help, because this finding may be present in patients with normal coronary anatomy. Exercise radionuclide studies improve predictive accuracy significantly, but once again, false-positive results are not infrequently reported.[28] A history of myocardial infarction has also been suggested as a criterion for inclusion in antianginal medication assessment. Unfortunately, in many cases, infarction is produced by the presence of isolated single-vessel coronary artery disease, and once infarction has occurred, the remaining coronary circulation may be entirely normal. Subsequent chest discomfort in such a person may have nothing to do with coronary occlusive disease.

Cardiac catheterization has long been considered the "gold standard" for assessment of coronary anatomy, with $\geq$60% narrowing considered sufficiently severe to produce symptoms of effort-induced coronary ischemia. However, assessment of coronary angiograms is subject to observer error, which may under- or overestimate the significance of a coronary artery narrowing when compared with autopsy specimens and does not definitely confirm a cause-and-effect relation between lesion and symptoms.[29] Presence or absence of collateral vessels, thickness of the myocardium,

pressures within the ventricle and concomitant valvular disease may also play roles in determining the "significance" of a coronary artery narrowing. Also, the presence or absence of coronary artery vasospasm further clouds this picture.

Coronary artery disease often occurs in the presence of other cardiac ailments that are capable of producing angina-like pain. In a patient in whom mitral valve prolapse, hypertrophic cardiomyopathy or pericardial disease is also present, symptoms attributed to coronary ischemia may indeed be the result of one of these other abnormalities. Additionally, diseases of the gastrointestinal, pulmonary, musculoskeletal and nervous systems may also produce symptoms that mimic or mask angina pectoris.

Thus, to confirm the presence of angina produced by coronary occlusive disease, it becomes necessary to confirm that symptoms truly result from an oxygen supply-and-demand imbalance caused by significant coronary occlusion. Catheterization, exercise testing using radionuclides and clinical evaluation to exclude the presence of other ailments capable of producing angina-like symptoms may be necessary to produce a pure cohort of patients for study.

Problems with Compliance

In long-term studies, it becomes difficult to confirm whether a patient has been taking the medications regularly and according to the specifications of the protocol. Patients are highly prone to skipping doses of the medication or taking the medication at incorrect time intervals. One is forced to rely on the integrity of the individual patient for accurate record-keeping in most cases. It is also important to keep accurate records of other antianginal medications prescribed for the patient. Should the study medication produce significant reduction in angina, patients may be tempted to reduce their intake of other antianginal agents, thereby producing data that underestimate the efficacy of the agent being tested. This further emphasizes the need for eliminating other antianginal medication from treatment regimens as a part of the study design.

Intake of nonmedicinal substances may also alter anginal patterns or disrupt the absorption or metabolism of the study agent. The time of ingestion of the study drug relative to meals may significantly affect absorption in some patients, and alcohol consumption may alter metabolism of substances that are degraded by the liver. Life-style alterations may also affect reported antianginal efficacy. When patients become aware of a drug's salutary effects, they may increase their level of activity in response to their increased "cardiac reserve." Thus, if a patient originally experienced angina after climbing 1 flight of stairs, he may now be able to climb 2 flights of stairs before experiencing angina. In both instances, the number of anginal attacks recorded will be equal, even though the study medications significantly improve functional capacity. Climatic changes may become significant in studies that extend beyond seasonal changes and result in variations in patient exposure to cold.

The Physician: Who Shall Test?

Through the design of the research protocol, an investigator's pretest bias or prejudice can be neutralized. Unfortunately, as discussed, it may be difficult to produce totally blind studies because of the perceptions of both the participants and the observers. In an era in which many research activities are sponsored by pharmaceutical companies that have spent millions of dollars developing a new medication, the desire of the investigator to show efficacy may significantly, albeit subtly, influence the outcome of the study. It is nevertheless imperative for the principal investigator to personally monitor quality control in the acquisition of data to assure consistency in the recording of both subjective and objective information. Accuracy is more likely to be obtained when the same observer is used throughout the entire study.

The greatest opportunity for prestudy bias or prejudice to occur is after the study is completed and the data interpretation begins. Inappropriate statistical manipulation, arbitrary exclusion of data that may be relevant but appears to be inconsistent with the mean and the drawing of broad conclusions based on a narrow range of data are errors that must be constantly avoided.

Conclusions

In summary, the ideal protocol, the ideal patient and the ideal investigator have not been found. In the assessment of antianginal medication, the subjective nature of this ailment, wide variability in the severity of coronary occlusive disease, poorly defined interactions with other agents and pretest study bias all contribute to the difficulty in determining effectiveness. It is unlikely that any investigator or group of investigators will ever produce a protocol applicable to all types of antianginal medications that will be universally convincing. Conclusions regarding the efficacy of any antianginal medication will undoubtedly continue to be predicated on assessments made by multiple independent investigators using a variety of research protocols, none of which is likely to be perfect.

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Activity of Transient Myocardial Ischemia Out of Hospital in Coronary Artery Disease and Implications for Management

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The management of patients with angina pectoris is based largely on the severity of symptoms, coronary anatomy and left ventricular function. The outcome for these patients is highly variable and depends largely on the degree of ischemic damage to the left ventricular myocardium. Recent work suggests that exercise-induced myocardial ischemia with or without angina is associated with a poor prognosis. Ambulatory monitoring of the electrocardiogram has revealed that most patients have frequent and prolonged episodes of transient ischemia out of hospital. These episodes are often asymptomatic and associated with ordinary everyday activities. In addition, ambulatory monitoring has demonstrated that transient ischemia during daily life has a circadian variation with exacerbations and peak density of ischemia in the first 4 to 6 waking hours of the day. Further studies have demonstrated that regional decreases in coronary blood flow occur during these ischemic episodes and have the same features seen out of hospital on continuous monitoring.

These newly noted characteristics of transient ischemia raise a number of practical questions for treatment. Is it necessary to relieve all ischemic activity quite apart from that which occurs with chest pain? Does present use of antianginal medication neglect the early morning increases in transient ischemia that occur, and are different dosage regimens required to treat ischemia adequately? Does suppression of all ischemic activity further protect myocardium and improve prognosis for the patient?

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The management of patients with angina pectoris and other manifestations of coronary artery disease (CAD) is lifelong and medical. Although surgery and angioplasty may be required in some patients, they do not replace the need for vigilance in the control of symptoms, risk factor modification, identification of high-risk groups for infarction or sudden death and continued strategies to prevent ischemic myocardial damage. The association of angina with ST-segment changes on the electrocardiogram (ECG) and increases in heart rate and blood pressure has led to the wide-scale use of exercise-induced ST-segment depression in the diagnosis, prognosis and therapeutic management of CAD. Although relief of symptoms and improvement in exercise performance are thought to be necessary to show treatment efficacy, clinicians have realized for years that angina pectoris is subjective, characterized by exacerbations and remissions in activity, known to occur at changing thresholds in different circumstances and mimicked by many other conditions.

There is now a growing realization that episodes of transient regional myocardial ischemia occur without symptoms and are not associated with exercise or increases in heart rate. Therefore, relief of symptoms and improved exercise tolerance in themselves may not prevent ischemic insult to the myocardium. The purpose of this article is to discuss some newly noted clinical features of ischemic heart disease as they apply to out-of-hospital patients engaged in their usual daily activities. These characteristics of disease activity may not be apparent from conventional testing and assessment of symptoms. They can be quantified objectively in individual patients and may represent features of the disease that require close surveillance and control in order to achieve the goals of prevention of myocardial damage and improved prognosis.

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Prognosis

Long-term clinical trials have shown that disturbances of left ventricular function (as manifested by decreased ejection fraction or symptoms of congestive heart failure), ventricular ectopic activity and angiographic extent of CAD (particularly left-main stenosis) are determinants of prognosis in patients with CAD.[1,2] Apart from the anatomic considerations of the extent of CAD and left ventricular damage, the presence of unstable angina, postinfarction angina or exercise tests markedly positive for ischemia (with or without chest pain) is now recognized as an adverse clinical sign. Few studies provide prognostic information for totally asymptomatic patients with CAD. In the U.S. Air Force study[3] of asymptomatic men with active ischemia by treadmill or radionuclide studies, a yearly mortality of 17% was noted. In both the National Institutes of Health[4] and Duke–Harvard studies[5] in mixed populations of symptomatic and asymptomatic patients, a considerable yearly mortality rate of up to 2 to 3% was found in the asymptomatic group overall. Many of these studies, however, were conducted in populations in which symptoms were both absent and present and have not emphasized whether there was evidence of continuing myocardial ischemia.

Fewer studies have addressed the prognostic implications of transient ischemia in patients with angina. Bonow et al[6] reported on patients with mild symptoms, ejection fractions at rest ≥40% and 3-vessel CAD. Those patients who had no objective evidence of transient regional myocardial ischemia on ECG or radionuclide ventriculogram had an excellent 4-year prognosis when contrasted with a comparable group with evidence of ischemia. These clinical markers of underlying transient myocardial ischemia (whether associated with pain or not) may represent a common pathophysiologic event resulting in damage to heart muscle and poorer prognosis quite apart from the extent of coronary disease and ventricular damage.

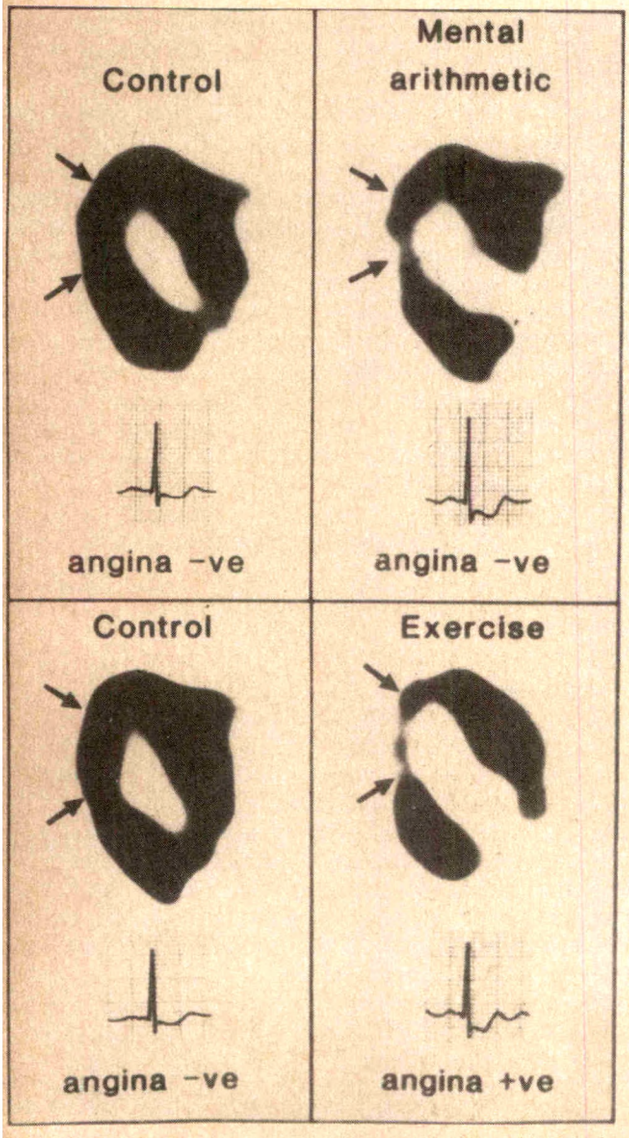

FIGURE 1. Regional myocardial perfusion assessed by positron emission tomography measuring rubidium-82 uptake. Left ventricle is shown with the mitral orifice posteriorly placed; **arrows** indicate the anterolateral wall of the left ventricle. Mental arithmetic caused a regional decrease in coronary blood flow, with silent ST-segment depression indicating ischemia. Later this abnormality recovered but was reproduced by supine exercise and associated with angina.

Transient Regional Myocardial Ischemia

Experimental and clinical research have both described in detail the sequence of events during episodes of transient ischemia: immediate failure of contractile function is followed by abnormalities of rhythm and electrocardiographic disturbances. On a biomechanical level, tissue oxygen and pH fall with failure of β oxidation, temporary preference for glycolysis and eventually, lactate accumulation. With time, membrane function and structure fail. These events have been characterized clinically in the hospital with the ECG, radionuclide ventriculography, thallium-201 imaging and positron emission tomography with substrates used as tracers.

Combining these techniques for detection of transient regional ischemia with such provocations as exercise, dipyridamole, ergonovine and exposure to cold has provided diagnostic and, recently, prognostic information regarding the presence of CAD. Deanfield et al[7,8] have studied patients with chronic stable angina, positive exercise tests for ischemia and known CAD with positron emission tomography. They have assessed regional myocardial perfusion using uptake of rubidium-82. They found perfusion defects in the same myocardial segments during both painful and painless episodes of ST-segment depression associated with exercise, cold exposure, mental arithmetic and cigarette smoking, as well as without provocation (Fig. 1). This evidence suggests that transient episodes of ST-segment depression do represent ischemic episodes in these patients and occur with activities associated with daily living. If the activity of transient ischemia affects clinical status and prognosis, then we need to know the trigger mechanisms, frequency and duration of events out of hospital.

New Clinical Features of Ischemic Activity

Twenty-four hour ambulatory monitoring of the ECG in patients with angina, exercise-induced ischemic ST-segment depression and proven CAD has been carried out in a number of research centers.[9–11] The results show that most episodes of myocardial ischemia as manifested by ST-segment depression during daily activity are asymptomatic (68 to 76%). The episodes are surprisingly prolonged; the median duration is 5 to 8 minutes and the range is from 1 to >60 minutes. Another striking finding in all these studies is that a large proportion of asymptomatic episodes occur during rest or are associated with such modest physical activities as eating, driving, light housework and mental arousal (Fig. 2). Deanfield et al[9] have shown that approximately one-half of these events have little or no increase in heart rate at the onset of ischemia and that the distribution of heart rates at onset of ST depression during ambulatory monitoring is lower than that seen in the same patients during exercise testing.

We recently demonstrated a significant circadian variation in the number and duration of ischemic episodes with a marked increase in ischemic activity during the first 4 to 6 waking hours of the day. The difference does not appear to be due to increased physical activity in the morning hours or markers of myocardial demand such as increased heart rate at onset of ST depression. These findings suggest that alterations in coronary tone and supply may be responsible for this morning peak in ischemic activity.

An increasing number of asymptomatic men undergo treadmill exercise and the "silent positive exercise test" indicates that myocardial ischemia remains a vexing clinical problem in these subjects. Ambulatory monitoring of the ECG has shown that most of these patients do indeed have multiple episodes of transient ischemia out of hospital. In addition, our data indicate that these ischemic events have all the same characteristics found in patients with angina (i.e., painless episodes, little or no tachycardia preceding events, prolonged duration and circadian rhythm).

Clinical Implications

A number of studies from major centers have demonstrated that silent myocardial ischemia in patients with CAD is more common than previously appreciated. At the same time, the activity of transient ischemia seems to be emerging as an adverse finding as it relates to prognosis. Although management with drugs, angioplasty and coronary bypass surgery are directed toward relief of symptoms, they are also used in an attempt to prevent or reverse the disturbances in coronary blood flow and ischemia that threaten ventricular myocardium. This new information about the characteristics of transient ischemia during daily activity suggests that important information regarding the activity of disease may be missed with assessment of symptoms and exercise response only.

Thus, a number of questions regarding therapeutic aims have been raised. Is it important to suppress all ischemic activity apart from the initial necessary step of relieving symptoms? Do the currently used dosage regimens of drugs take into account the circadian variation of ischemia and the surge of activity in the morning? What are the differential effects of various drugs on the different types of transient ischemia seen out of hospital? Will the activity of transient ischemia help to identify high-risk groups who require more aggressive evaluation and treatment?

With ambulatory electrocardiographic recording it is possible to quantitate previously unnoticed episodes of disturbed regional myocardial perfusion and correlate these with the activities provoking them. It seems unlikely that transient regional myocardial ischemia in any form can be dismissed as unimportant. However, caution is suggested before the wide-scale application of ambulatory monitoring in the assessment of CAD occurs. Most studies have been done in relatively homogenous groups with symptomatic coronary dis-

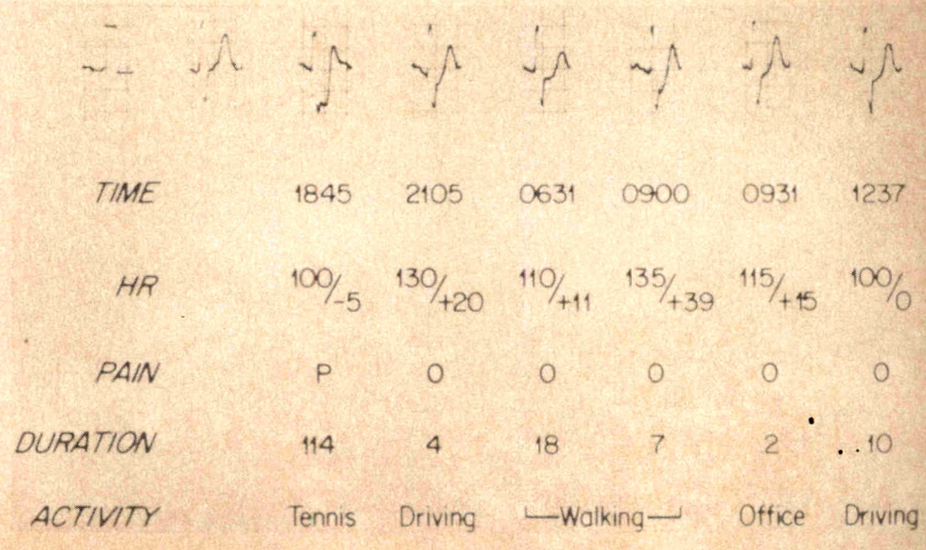

FIGURE 2. A typical 24-hour ambulatory electrocardiographic recording in a 61-year-old man showing electrocardiographic complexes from 6 episodes of transient ischemia, only 1 of which was accompanied by angina. The time of each episode and the heart rate (HR) at onset and change in HR 1 minute before onset are shown below each episode. Three of the events were prolonged, lasting for 10 minutes or longer. Most episodes were associated with ordinary everyday activity.

ease. The prevalence of silent transient ischemia and the sensitivity and specificity of ambulatory ST-segment depression to detect ischemia in a more heterogenous population are unknown. The day-to-day variability and natural history of exacerbations and remissions in disease activity must be considered when assessing the effect of an intervention on ambulatory ischemia. Prospective studies and clinical trials will be needed to answer these questions.

In summary, in the natural history of coronary atherosclerosis, 25 to 30% of myocardial infarctions and sudden deaths are silent or unexpected manifestations of coronary heart disease. To this we can now add ambulatory transient ischemia, which appears to be common, surprisingly prolonged and associated with ordinary daily activities. The underlying transient decreases in regional coronary flow suggest that the activity or reactivity of atherosclerotic and stenosed epicardial arteries plays a causative role and needs more attention. If clinical research shows that this ischemic activity is undesirable, then the goals of treatment must change. The practitioner may have to modify his approach to assessment and management of these patients by seriously considering the activity and characteristics of ischemic heart disease out of hospital and during daily life in an attempt to procure lasting relief of symptoms and prevention of ischemic damage.

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Mechanisms and Therapy of Silent Myocardial Ischemia and the Effect of Transdermal Nitroglycerin

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Studies of the mechanisms and characteristics of ischemic heart disease have increasingly documented evidence of myocardial ischemia in the absence of symptoms. Recent work using objective criteria of ischemic events has confirmed that angina pectoris or its equivalents need not accompany true myocardial ischemia, and this appears to be quite common. The impact of these findings on prognosis awaits further study, but preliminary data suggest an improved prognosis for persons in whom coronary artery disease remains asymptomatic compared with symptomatic patients. Further, reduction of silent ischemic events with nitrate therapy may be associated with a more benign subsequent course. Preliminary trials show a reduction of the number, duration and magnitude of silent ischemic events by transdermal nitroglycerin. Ongoing technical innovations in monitoring systems should allow more complete characterization of this syndrome and lead to definition of medical therapy for it. (Am J Cardiol 1985;56:23I–27I)

Several acute ischemic syndromes have recently been defined in terms of their pathophysiology, and this has facilitated the choice of more specific therapy. For example, the recognition that transmural acute myocardial infarction represents an occlusive clot in a main coronary artery[1] has led to the use of either streptokinase or tissue plasmin activator as fibrinolytic therapy.[2,3] In addition, nontransmural acute myocardial infarction, unstable angina pectoris, stable exertional angina pectoris, stable spontaneous angina and variant angina pectoris have also been defined. A new syndrome—silent myocardial ischemia—has also been noted. This article will focus on selected aspects of silent myocardial ischemia and will discuss the use of transdermal nitroglycerin to control the number, duration and magnitude of ischemic events.

Definition of Acute Ischemic Syndromes

Transmural myocardial infarction is a syndrome associated with chest pain, ST-segment elevation, Q-wave evolution and appearance of cardiac enzyme activity in plasma. DeWood et al[1] have demonstrated that this syndrome is associated with an occlusive clot in 87.3% of patients with transmural myocardial infarction, although Oliva et al[4] have shown that spasm of the coronary artery can cause transmural acute myocardial infarction in selected patients. In the Framingham experience,[5] 15% of transmural myocardial infarction occurred silently. Further, the incidence of silent myocardial infarction appears to be 3.6/1,000 adults compared with an incidence of 5.3/1,000 symptomatic infarcts.[6] Thus, silent transmural myocardial infarction appears to be a frequent event.

The precipitating events leading to nontransmural acute myocardial infarction are the least well known of the acute ischemic syndromes. The syndrome, which consists of chest pain, ST-segment changes on the electrocardiogram and the appearance of cardiac enzyme activity in plasma, is initiated by an admixture of clot, spasm, platelet aggregation and inappropriate myocardial oxygen demand. The incidence of silent nontransmural acute myocardial infarction is unknown, but autopsy evidence suggests that between 20 and 60% of acute myocardial infarctions are symptomatic.[7] Thus, silent nontransmural acute myocardial infarction may be quite common.

Stable exertional angina pectoris was described by Heberden in 1772. The classic syndrome of exertional chest pain relieved by rest and nitroglycerin is caused by an increase in myocardial oxygen demand, which outstrips flow through fixed coronary arterial obstruction. Even in this classic syndrome, silent events have been described. It is well known that silent ST-segment depression frequently occurs during exercise testing in patients with established coronary arterial obstruction. In addition, silent ST-segment depression during spontaneous exertion has been described

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using Holter monitoring. Cecchi et al,[8] for example, have described silent ST-segment depression with exertion in patients with classic exertional angina documented by ambulatory monitoring. They found that the silent events were more frequent than the symptomatic events. These observations support an earlier report by Coccol et al[9] that showed that silent ischemic events induced by exertion are more frequent than symptomatic events in patients with classic exertional angina.

Spontaneous angina pectoris is a syndrome associated with chest pain and reversible ST-segment depression. The symptoms occur at rest with emotion or with minimal activity. This syndrome is characterized by the poor correlation of symptoms with an increase in myocardial oxygen demand. The syndrome has been called unstable angina, angina at rest, emotional angina, coronary insufficiency and preinfarction angina,[10–14] depending on the particular characteristic under discussion. The term "spontaneous angina" will be used here to stress the lack of correlation of external events with an increase in myocardial oxygen demand and the potential initiating mechanisms. The incidence of silent events in this syndrome is incompletely defined but appears to be quite significant. Biagini et al[15] documented 520 episodes of ST-segment changes in 11 patients who fit the profile of spontaneous angina, and only 12% of the episodes were symptomatic.

Spontaneous Angina: A Disease of Decreased Myocardial Oxygen Supply

A specific sequence of changes occurs in patients with spontaneous angina. The sequence includes ST-segment alteration (either elevation or depression), increase in pulmonary artery pressure, increase in blood pressure and finally chest pain. The chest pain is a relatively late event in the sequence of the ischemic process.[16] Also, it can be demonstrated that coronary sinus oxygen saturation decreases before the ST-segment changes,[17] indicating that regional perfusion falls before the ischemic event. In most instances of spontaneous angina, ischemia precedes the increase in myocardial oxygen demand.

Because the onset of ischemia precedes the onset of increased oxygen demand, spontaneous angina must be associated with a reduction in oxygen supply as the initiating event. The fall in oxygen saturation in the coronary sinus in the early moments of the event[17] and before the ST-segment alteration further confirms the decrease in regional perfusion associated with a spontaneous anginal event. A primary decrease in coronary blood flow appears to be the initiating event in the cascade of temporal changes associated with spontaneous ischemic events.

The discussion of spontaneous ischemia and the subsequent discussion of spontaneous silent ischemia depend on the assertion that ST-segment alterations reliably reflect ischemic events. Although not completely understood in all situations, recent evidence suggests that, in patients with atherosclerotic coronary artery disease (CAD), the overwhelming proportion of ST-segment events indicate ischemia. For example, Maseri et al[18] have shown that patients with spontaneous ST-segment depression demonstrate a thallium defect, which occurs during the periods of ST-segment change both with and without chest pain. Recently, Deanfield et al,[19] using rubidium imaging and positron emission tomography, have shown that spontaneous ST-segment events, both symptomatic and asymptomatic, are invariably associated with a reduction in regional perfusion. In patients with CAD, there is little evidence that sustained ST-segment alterations >60 seconds occur without a reduction in regional blood flow.

Potential mechanisms that could initiate intermittent reduction of regional blood flow include spasm of the coronary artery,[20] platelet aggregation with subsequent displacement or lysis of the platelet clot[21] and alteration of coronary artery distending pressures.[22] These mechanisms occur in diseased coronary arteries, providing a physiologic basis for initiation of episodes of spontaneous reduction in blood flow.

Spontaneous angina reflects intermittent reduction of coronary blood flow. It is a disease of reduced blood flow and not of increased myocardial oxygen demand. Prevention and treatment of spontaneous ischemic events should be planned with an understanding of these pathophysiologic mechanisms.

Silent Myocardial Ischemia: Definition and Demonstration

Silent myocardial ischemia can be defined as the presence of objective evidence of ischemia without accompanying symptoms in patients with anatomically significant CAD.[23] This definition can be expanded to include objective evidence of ischemia in patients both with and without coronary atherosclerotic obstruction—again occurring without symptoms. Several objective markers of imbalance between myocardial oxygen demand and supply have been proposed, including anatomic obstruction to flow, electrocardiographic changes, distribution of radioactive tracers or coronary blood flow[24] and biochemical indicators of inadequate blood flow.[25] Each of these markers has been used to document the existence of the ischemic process unaccompanied by the pain of angina pectoris.

Hemodynamically significant CAD has been repeatedly documented in asymptomatic patients. In one review, Diamond and Forrester[26] indicated that asymptomatic CAD existed in 4.5% of patients autopsied after death from noncardiac causes. Erikssen et al[27] documented hemodynamically significant CAD with angiography in 3.4% of a group of asymptomatic and presumably healthy men. Froelicher et al[28] found significant CAD with angiography in 2.4% of his cohort of asymptomatic U.S. Air Force men. Cohn analyzed these data and reported an overall population rate of asymptomatic yet hemodynamically significant CAD between 2 and 5%.[23]

Asymptomatic ischemia has been detected by continuous ambulatory electrocardiographic monitoring, using alterations of the ST segment as the marker of the myocardial ischemia. In 1974, Stern and Tzivoni,[29] using high-fidelity Holter recording systems, studied

80 patients with symptoms of angina pectoris; 37 patients demonstrated ST-segment changes during the monitoring period. In 24 of the 37 patients, ST-segment change occurred both with and without symptoms. Symptomatic events in this cohort of 24 patients were usually associated with ST-segment alterations. Importantly, 13 of the 37 patients experienced episodes of ST-segment alteration without chest pain. This study suggested that in patients with anginal episodes, asymptomatic episodes of ST-segment changes frequently occur.

Schang and Pepine[30] in 1977 reported that 75% of the episodes of ischemic ST-segment depression on continuous ambulatory electrocardiographic monitoring in their patients with CAD were asymptomatic and that 72% of these asymptomatic events occurred at rest or with minimal activity. Moreover, hourly nitroglycerin significantly decreased the frequency of these episodes, supporting the concept that these events represent painless ischemia. Coccol et al[9] found ST-segment changes in 22 of his 40 patients with CAD and stable effort angina. Most of the events were asymptomatic; the symptomatic events were less frequent but lasted longer than the asymptomatic ones. Cecchi et al[8] described 32 patients with established CAD and effort angina who had ST-segment depression on continuous ambulatory electrocardiographic monitoring; 8 of these patients always had pain with ST-segment depression, no patient ever had pain with ST-segment change and 15 had both symptomatic and asymptomatic events. In the last group of patients, both the duration and extent of ST-segment depression were greater when accompanied by angina. Recently, Nademanee,[31] and Deanfield[32] and their co-workers, using quantitative systems for analyzing continuous ambulatory electrocardiographic monitoring, demonstrated that between 70 and 80% of ST-segment events in patients with established CAD occur without symptoms. These observations suggest that silent ST-segment alterations are frequent in patients with established CAD, probably reflecting recurrent silent ischemic events in such patients.

Silent ischemic events may also occur in patients with angiographically normal coronary arteries, reflecting either spontaneous increases in coronary vascular tone or inordinate increases in myocardial oxygen demand. Guazzi et al[33] described, in a single patient, episodes of silent ST-segment alterations with hemodynamic changes consistent with anginal episodes; the patient had angiographically normal coronary arteries. Masseri[16] in 1978 performed continuous ambulatory electrocardiographic monitoring in patients with angina at rest and noted a large number of transient ST-segment alterations; 10% of these patients had angiographically normal coronary arteries. These studies suggest that transient ischemic events can occur in patients without obstructive CAD.

ST-Segment Alterations as a Marker of Myocardial Ischemia

Several investigators have urged caution in the use of ST-segment depression during continuous electrocardiographic monitoring as a marker of asymptomatic myocardial ischemia for several reasons, including nonischemic induction of ST-segment changes and artifact induced by recording systems. Armstrong et al,[34] using 2-channel system (Avionics) and an unknown duration of ST-segment alteration as an index, reported >1 mm of ST-segment depression in 15 of 50 normal asymptomatic subjects. The episodes lasted 30 seconds to 2 hours, but there were no subsequent stress electrocardiographic abnormalities or morbid events during the 36 month follow-up period.

Crawford et al,[35] using single-channel recording system (Avionics) and a 3-beat criterion, reported a 39% false-positive rate when comparing ST-segment depression on continuous ambulatory electrocardiographic monitoring with angiography.

Suggested causes of ST-segment depression in the absence of myocardial ischemia include dynamic changes in autonomic tone, electrolyte abnormalities, various drugs, cerebrovascular disease,[35] hyperventilation, large carbohydrate meals, orthostatic position changes, mitral valve prolapse, neurocirculatory asthenia[36] and thermal, physical and emotional stress.[37] These episodes tend to be prolonged, with gradual onset and gradual regression. However, most investigators, including Armstrong and Morris,[36] have clearly considered silent ST-segment depression to reflect myocardial ischemia in patients with typical angina and probably to reflect ischemia in patients with known CAD. Substantial work with true normal subjects using artifact-free recording systems will be required to assess the incidence and implications of silent spontaneous ST-segment depression in otherwise normal subjects. Our own experience—using a calibrated real-time recording system and a 60-second ST-segment criterion and characterization of ST-segment changes with discrete onset and offset as indicative of ischemia—suggests that ischemic ST-segment events in normal subjects without prolapsed mitral valve are very infrequent.

Maseri et al,[16] concerned with the implication of spontaneous ST-segment depression as a marker of ischemia in patients both with and without atherosclerotic vascular disease, have investigated the implication of these changes. In 7,000 continuous electrocardiograms in patients with a history of spontaneous angina, with and without angiographically defined CAD, they noted numerous typical ST-segment changes not associated with anginal pain. A large number of asymptomatic ST-segment changes were accompanied by hemodynamic left ventricular dysfunction and by regional reduction of myocardial perfusion demonstrated by thallium scanning. Chierchia et al[38] have shown that silent ST-segment changes are preceded by regional myocardial blood flow reduction, based on continuous monitoring of coronary sinus oxygen saturation. Maseri et al[16] have also shown the association of asymptomatic transient ST-segment changes with angiographically defined vasospasm in patients with and without coronary artery disease. Finally, Deanfield et al,[19] using rubidium imaging with positron emission tomography, have demonstrated

that each episode of ST-segment alteration is associated with a decrease in regional perfusion of the myocardium. To date, there has not been a demonstration that a spontaneous ST-segment change >60 seconds in patients with CAD occurs in the absence of a reduction of coronary blood flow.

Thus, while the usefulness of the ST-segment change as a marker of myocardial ischemia in completely asymptomatic normal persons without CAD may still be in some doubt despite ongoing technical innovations in monitoring techniques, ST-segment abnormalities in patients with previous anginal symptoms or a history of CAD seem to represent myocardial ischemia, even in the absence of angiographically defined disease or pain during a given ST-segment event.

The Prognostic Implications of Silent Myocardial Ischemia

The prognosis of silent myocardial ischemia is poorly defined; both an increased mortality secondary to a defective anginal warning system and a decreased mortality related to a smaller potential ischemic zone have been proposed.[23] Cohn et al[39] have followed a group of 127 symptomatic patients and a smaller cohort of 44 asymptomatic patients with similar CAD for more than 7 years. The survival at 7 years was 81% in the asymptomatic group compared with 62% in the symptomatic group; the yearly mortality was 2.7 compared with 5.4%, respectively. In the patients with 3-vessel disease, the yearly mortality rate in the asymptomatic group was 4.7% compared with 8.7% in the symptomatic group. This suggests an intermediate prognosis for silent ischemia in persons with symptomatic CAD compared with those without CAD. This study represents the largest cohort of asymptomatic subjects followed; however, not all of the asymptomatic patients had had documented silent myocardial ischemic events. Clearly, further data are necessary concerning the natural history and prognostic implications of silent myocardial ischemia and the effects of therapeutic reduction in the frequency of silent ischemic episodes. In addition, there is a paucity of data defining the outlook for patients with angina who also demonstrate silent myocardial ischemic events; our initial experience suggests that these patients have an adverse short-term prognosis in the absence of therapy.

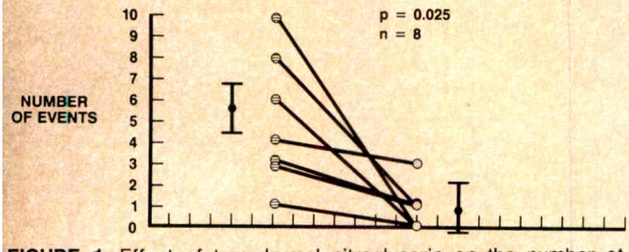

FIGURE 1. Effect of transdermal nitroglycerin on the number of ischemic events. Both symptomatic and asymptomatic events are included in number of events. ⊖ represents patients before therapy; ⊙ represents patients after stabilization on transdermal nitroglycerin.

The Abolition of Silent Ischemia by Nitrates

The treatment of silent ischemic events is largely unexplored. There are a number of potential agents that could abolish these events, including nitrates, β-blocking agents, calcium-channel blocking agents and coronary bypass surgery. We have been examining the use of transdermal nitroglycerin in the syndrome of silent myocardial ischemia. There were several reasons for the choice of this agent. The nitrates have a long history in the treatment of spontaneous anginal events, and silent ischemia is analogous to spontaneous angina. Transdermal nitroglycerin could provide nearly constant blood levels, which may be necessary in patients with silent ischemia because they do not know when they experience ischemic events. In addition, the nitrates have a known safety range without decreasing myocardial contractility, so we could titrate to large doses if necessary to treat the silent events.

Schang and Pepine[30] studied the effects of sublingual nitrates compared with placebo on the frequency of silent myocardial ischemic events. Five patients were treated with either hourly sublingual nitroglycerin or placebo during 10-hour periods of ambulatory monitoring. Asymptomatic episodes of ST-segment depression were significantly less frequent with nitrate therapy than with placebo (3.7 compared with 0.6 episodes per monitoring period).

We have recently completed an open label trial to test the effects of transdermal nitroglycerin on the

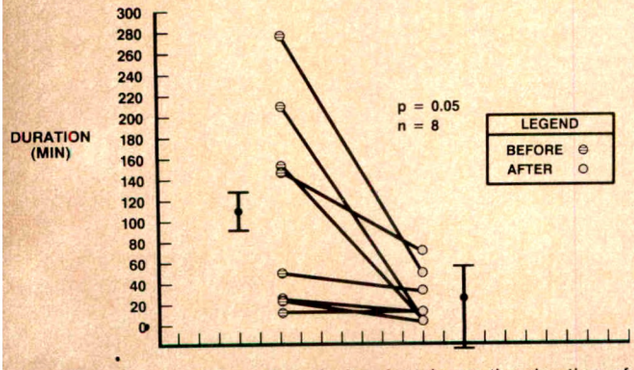

FIGURE 2. Effect of transdermal nitroglycerin on the duration of ischemic events.

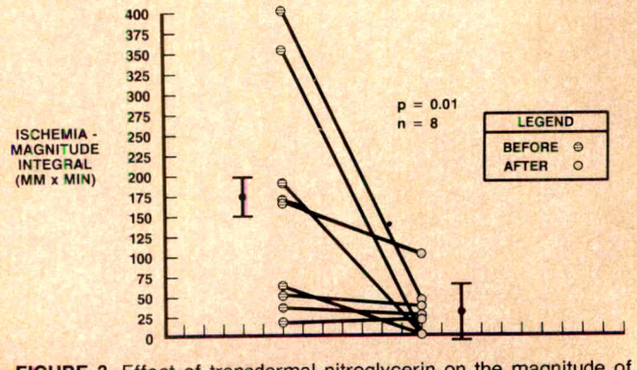

FIGURE 3. Effect of transdermal nitroglycerin on the magnitude of ischemic events as estimated by the ischemia-magnitude integral.

number, duration and magnitude of ischemic events.[40] In 8 patients with chronic stable angina, we performed 24-hour ambulatory monitoring using a calibrated system (DMI Instruments). From each tape a 24-hour full disclosure record was displayed on hard copy. From the hard copy printout, the onset and offset of each ST-segment event (either depression or elevation) were marked. In addition, the maximal depth of either the depression or elevation was measured in millimeters. We then counted the number of events, measured the duration in total minutes and estimated the magnitude of each event by multiplying the duration by the magnitude for each event—the so-called ischemia-magnitude integral. The baseline 24-hour tape was obtained while patients were receiving β blockade and sublingual nitroglycerin. Each patient was experiencing symptomatic angina pectoris on the regimen of β blockade and sublingual nitroglycerin.

We then titrated the dosage of transdermal nitroglycerin in each patient, beginning with 5 mg/24 hours (10 cm^2) and increasing the dose in 5 mg/24 hour increments. We increased the dosage until the number of symptomatic events was abolished and the 24-hour tape was repeated. The mean dosage was 10.4 mg/24 hours (range 5 to 20 mg or 10 to 90 cm^2). The number of symptomatic events decreased in all 8 patients. In addition, the total number of events fell from 5.8 to 0.9/24 hours (Fig. 1, $p < 0.025$). As in other studies, 80% of the events were silent.

The duration of ischemic events also decreased from 110 to 21 minutes/24 hours (Fig. 2, $p < 0.05$). The magnitude of the ischemia as estimated by the ischemia-magnitude integral also decreased (Fig. 3, $p < 0.01$).

Thus, in an open label trial, using a titration protocol, transdermal nitroglycerin reduced the number, duration and magnitude of both symptomatic and asymptomatic ischemic events. We are currently performing a double-blind, placebo-controlled trial to confirm these initial results. In addition, we are assessing the impact of attenuation by the time of this therapeutic result. Each of the agents that could potentially reduce the number of ischemic events defined by ambulatory monitoring should be subjected to rigorous examination. Our initial results with transdermal nitroglycerin are promising and suggest a role for these agents in controlling silent myocardial ischemia.

In summary, silent myocardial ischemia is a common manifestation of ischemic heart disease and occurs in all the ischemic syndromes. The current diagnostic standard for silent ischemia involves ambulatory monitoring. There is a paucity of data concerning the treatment of silent ischemic events. Our initial data suggest that transdermal nitroglycerin given in sufficient doses can reduce the number, duration and magnitude of ischemic events.

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Nitrate Tolerance

JOHN O. PARKER, MD

Nitrate tolerance may be defined as that condition in which increasing nitrate doses are required to induce a given hemodynamic or antianginal effect. Tolerance may be due to changes in pharmacokinetics or to alterations in the property of target tissues, making them less sensitive to the nitrate effect. The question of nitrate tolerance has been addressed using 4-times-a-day therapy with oral isosorbide dinitrate, daily therapy with long-acting isosorbide dinitrate ointment and once-a-day therapy with nitroglycerin patches. Each of these treatment modalities is associated with initial beneficial effects, but during sustained therapy, there is marked attenuation of the effect both in magnitude and duration. Thus the concept that stable nitroglycerin blood levels over 24 hours are desirable appears to be incorrect. Preliminary hemodynamic studies suggest that short periods of nitrate withdrawal restore the hemodynamic effect of the nitrates, and it is postulated that intermittent nitrate therapy may be desirable in the management of angina. Transmucosal nitroglycerin administration for a 15-hour period with a 9-hour washout period was recently undertaken. The results demonstrated that this method of nitrate administration is not associated with development of tolerance to its antianginal effects.

Large doses of transdermal nitroglycerin, varying from 45 to 100 mg during short-term studies, have been shown to result in only minimal increases in exercise tolerance at 24 hours. These findings, plus evidence that with smaller doses tolerance occurs after only 1 week of once-a-day therapy, challenge the concept that larger nitroglycerin dosages, administered once a day by transdermal patches, could be effective throughout a 24-hour period in patients with angina pectoris. The current information suggests that it would be necessary to apply larger doses, but to remove them after a period of 12 to 14 hours and allow a washout period to prevent tolerance.

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Nitrate tolerance may be defined as that condition in which increasing nitrate doses are required to induce a given hemodynamic or antianginal effect. Tolerance may be due to changes in pharmacokinetics or to alterations in the property of target tissues, making them less sensitive to the nitrate effects. There is substantial evidence of the development of tolerance to the organic nitrates. This has been demonstrated in munitions workers,[1] patients with angina pectoris[2,3] and patients with left ventricular dysfunction.[4] The fall in systolic blood pressure after the administration of nitrates has been shown to be markedly attenuated during sustained therapy in animals,[5] patients with angina[3] and patients with heart failure.[4] The effect of these agents on left ventricular filling pressures in cardiac failure persists during sustained therapy, but the magnitude of response is diminished.[4,6]

There has been substantial controversy as to the relevance of hemodynamic tolerance to the antianginal effects of the organic nitrates. Clinical studies have reported prolongation of exercise times for periods of several hours after oral isosorbide dinitrate (ISDN) during sustained therapy.[7,8] Our studies have repeatedly shown that during 4-times-a-day oral therapy with ISDN, the antianginal effects persist for only 1 to 2 hours, rather than the 8 hours seen during acute dosing.[2,3,9] The basis for these conflicting observations is not clear but may be related to study design.

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Tolerance to Isosorbide Dinitrate

Twelve male patients with chronic stable angina entered a placebo-controlled, double-blind study in which the hemodynamic and antianginal effects of ISDN were studied during short- and long-term therapy.[2] During the short-term phase, each patient was

studied twice a week with at least 2 days separating study days. Following preliminary treadmill exercise testing, patients were given identical-appearing tablets that contained either placebo or ISDN in doses of 15, 30, 60 or 120 mg. Each patient received placebo on 2 occasions. Investigations were carried out in the morning; patients were in the fasting state and heart rate and blood pressure were recorded in the supine and standing positions. Patients then performed treadmill testing, and the times to the onset of angina and development of moderate angina were recorded. Immediately after this control test, the scheduled medication was administered, and resting hemodynamic indexes were measured and treadmill exercise was performed after 1, 2, 4, 6 and 8 hours. All 12 patients received 15, 30 and 60 mg of ISDN, but only 7 received the 120-mg dose in this short-term phase, as headache or hypotension developed with 60 mg in 5 patients.

After completion of the short-term phase, patients were placed on placebo tablets 4 times a day for 2 weeks. At the end of this period, hemodynamic and treadmill exercise testing were carried out before and 8 hours after the final morning dose of placebo. In consecutive weeks, patients received 15, 30, 60 and 120 mg of active ISDN 4 times a day (at 8 AM and 12, 4 and 8 PM). At the end of each of these treatment periods, the patients came to the laboratory without taking the morning medications. Treadmill exercise testing was performed, the scheduled dose of ISDN administered and then hemodynamic and treadmill exercise testing performed over an 8-hour period.

During short-term therapy with each dose of ISDN, systolic blood pressure dropped at 1 hour and remained below placebo values for the 8-hour observation period. There was an apparent dose-response relation with greater decreases in systolic blood pressure with the higher doses. This hypotension was accompanied by reflex increases in heart rate. During long-term therapy, each dose of ISDN produced a reduction in systolic blood pressure at 1, 2 and 4 hours, but not at 6 or 8 hours. There was no apparent dose-response relation.

During the short-term study, significant prolongation of treadmill exercise time to the onset of angina and development of moderate angina was seen with each dose of ISDN. This effect, which was greater with the larger doses, was apparent over the entire 8-hour observation period. During long-term, 4-times-a-day therapy, exercise times to the onset of angina and development of moderate angina were prolonged for only 2 hours after each dose, and thereafter, there was no difference compared with placebo. The magnitude of the improvement seen at 2 hours was less pronounced than that seen during short-term therapy. The attenuated hypotensive and antianginal effects occurred despite the presence of significantly higher plasma ISDN concentrations during the long-term compared with the short-term study.

Since this initial observation, we have completed further studies that have confirmed the development of tolerance: treadmill exercise time is prolonged for 2 hours after a given dose, but no effect is seen thereafter.[3,9]

Tolerance to Transdermal Isosorbide Dinitrate

In a recent study, we documented the development of tolerance to other modes of ISDN administration.[10] Twelve patients were studied after the single application of 100 mg of ISDN ointment spread over a 200 cm^2 area. This preparation was formulated to provide an effect over a 24-hour period. This investigation showed that treadmill walking time was prolonged for 8 hours after a single application, but there was no effect at 24 hours. When similar doses were applied once a day for a period of 7 to 10 days, treadmill walking time over the 8-hour period was identical to that seen with placebo ointment. This was further confirmation of the rapid development of tolerance during long-term therapy. When sublingual nitroglycerin (NTG) was administered, a normal hypotensive response was seen and there was a marked improvement in treadmill walking time.

Tolerance to Transdermal Nitroglycerin

NTG ointment has been used for several years for the management of patients with angina[11] and congestive heart failure.[12] Studies have shown prolongation of treadmill walking time for periods of 3 to 7 hours[11,13] with this product, but little information is available regarding long-term therapy. Reichek et al[11] studied a small subgroup of patients after several months of 3-times-a-day therapy with NTG ointment and found no attenuation of the antianginal effects. There are, however, no well-controlled studies that have assessed the antianginal effect of NTG ointment during long-term therapy.

NTG patches have been available for approximately 3 years in the United States and they have received widespread clinical acceptance. The patches are designed to provide a steady infusion of NTG and to lead to stable plasma concentrations over the 24-hour dosing interval. The early studies claimed that patches delivering 5 mg over 24 hours induced plasma NTG concentrations of approximately 1 ng/ml.[14] Subsequent investigations have not confirmed this; generally, the patches produce much lower plasma levels.[15]

Clinical studies have shown that during short-term therapy with NTG patches, exercise tolerance is prolonged for periods ranging from 4 to 8 hours, but with the usual doses used, there have been no reports of prolongation for longer periods throughout the 24 hours.[15,16] In a group of 6 patients who received 45-mg patches, we did show a 24-hour effect during short-term therapy (Fig. 1), but no data are available regarding long-term therapy.[15] In an uncontrolled study, we observed 4 patients before and after applications of 50- to 100-mg NTG patches and found effects at 12 and 24 hours in 3 patients.

We have demonstrated that during long-term therapy there is attenuation of the antianginal effects with

the currently available doses of transdermal NTG. Thus, after 7 to 10 days of once-a-day therapy with NTG patches that deliver 15 mg/day, treadmill walking time throughout the testing period was similar to that seen with placebo.[15]

It would appear from the data from oral ISDN, transdermal ISDN and transdermal NTG studies that long-term therapy with each of these nitrate preparations is associated with diminution of the hemodynamic and antianginal effects. The complete lack of efficacy of transdermal ISDN and transdermal NTG during long-term therapy suggests that the concept of providing steady-state plasma levels for continuous antianginal protection is incorrect.

Rate of Tolerance Development

The studies just outlined have demonstrated that tolerance to the antianginal effects of the nitrates occurs within 7 to 10 days of sustained therapy. There is little information regarding the minimal period of time required for such tolerance to develop in man.[17] We used a challenge with 5 mg of sublingual ISDN to assess nitrate responsiveness (Fig. 2). On day 1, the effect of sublingual ISDN (5 mg) on heart rate and systolic blood pressure was assessed over a 3-hour period. Patients then received 15 mg of ISDN every 6 hours for 48 hours. On day 2, after only 3 tablets of ISDN, the hypotensive effect of sublingual ISDN was attenuated. The reduction in systolic blood pressure was approximately 50% of that present during the control study day. A similar pattern was seen on the third day, 48 hours after the institution of oral ISDN therapy. Patients were then placed on oral ISDN placebo, and on day 4, when they had received only 3 placebo tablets, the blood pressure response to sublingual ISDN was similar to the control values. The response persisted on day 5. This study demonstrated that within less than 24 hours there was evidence of hemodynamic tolerance, and that within less than 24 hours of withdrawal of oral ISDN the hemodynamic response to the ISDN challenge was normal.

Is Intermittent Nitrate Therapy Less Likely to Be Associated with Nitrate Tolerance?

As demonstrated, the delivery systems designed to produce steady-state nitrate levels are associated with complete loss of antianginal efficacy in a short period of time. When oral medications are given 4 times a day, the antianginal effect is diminished but is still evident. It has been suggested that a period of drug washout might prevent the development of tolerance. We assessed this by comparing the antianginal effects of oral ISDN administered 4 times a day with transmucosal NTG administered 3 times a day, which provided a 9-hour washout period overnight.[9] This study confirmed the development of tolerance during sustained, 4-times-a-day therapy with ISDN. This study showed that treadmill walking time was prolonged 1 hour after a given oral ISDN dose, but no subsequent effect was seen. On the other hand, when buccal NTG was given 3 times a day with a 9-hour washout period, treadmill exercise time was prolonged for a period of 5 hours after a single dose. The response during therapy with transmucosal NTG was similar during the short- and long-term phases of this study. Recent studies from Germany suggest that single daily doses of sustained-release oral ISDN are not associated with tolerance, whereas more frequent dosing is associated with marked diminution of the antianginal effects.[18]

At the present time, it appears desirable to prescribe oral nitrates on a 3-times-a-day basis, with no medication after the supper dose. With transdermal preparations, one could postulate that it would be best to remove the patches after 12 to 16 hours of application to allow overnight washout.

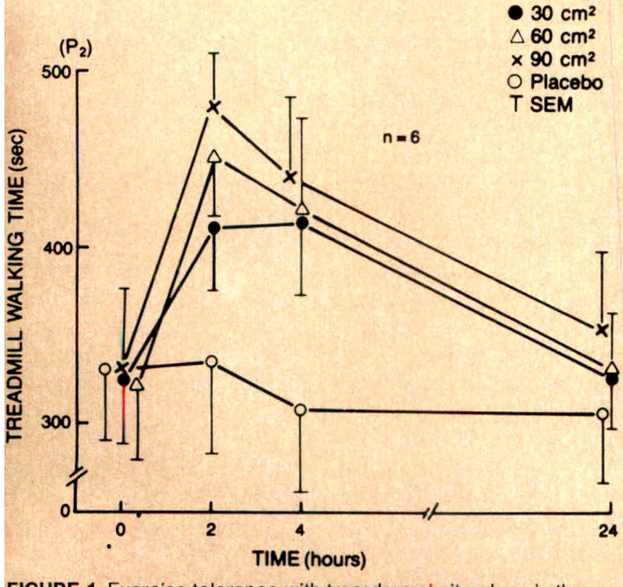

FIGURE 1. Exercise tolerance with transdermal nitroglycerin therapy (acute). Reproduced with permission from Am J Cardiol.[15]

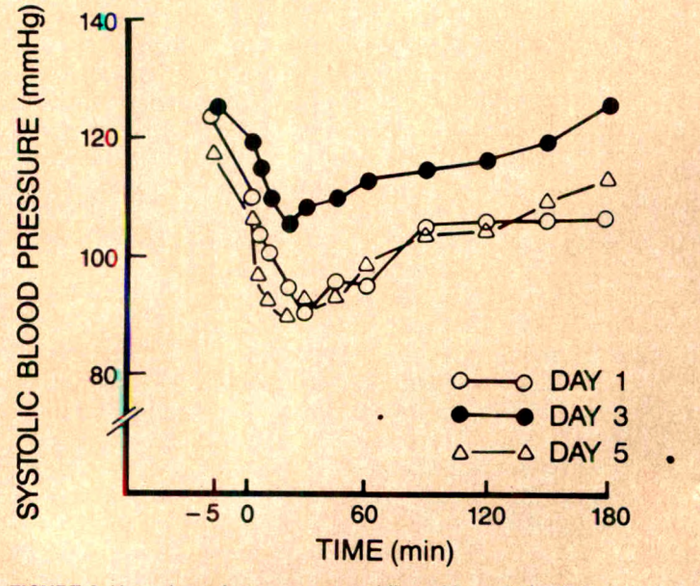

FIGURE 2. Hemodynamic response to sublingual isosorbide dinitrate challenge. Reproduced with permission from Circulation.[17]

In summary, studies have clearly documented the organic nitrates to be potent vasodilators and to induce major hemodynamic and antianginal effects. During sustained therapy with oral ISDN, transdermal ISDN and transdermal NTG, the hemodynamic and antianginal effects are attenuated. Nitrate tolerance has been shown to develop promptly but can be reversed during short periods of nitrate withdrawal. Intermittent low-dose nitrate therapy is suggested to produce prolonged clinical effects without development of clinically relevant tolerance to the hemodynamic and antianginal effects.

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Hemodynamic Attenuation and the Nitrate-Free Interval: Alternative Dosing Strategies for Transdermal Nitroglycerin

JOHN T. FLAHERTY, MD

Various dosing strategies to determine therapeutic effects of nitroglycerin (NTG) preparations are reviewed. The importance of individual patient titration in establishing an effective NTG dosage is emphasized by reviewing a nitroglycerin ointment study and a crossover study. Studies reporting the development of hemodynamic attenuation ("tolerance") with long-term nitrate therapy are also discussed. The results of these and other studies suggest that the magnitude of the hemodynamic response to NTG or isosorbide dinitrate diminishes over time, with acute or first-dose effects far exceeding those obtained during long-term therapy. However, patients on long-term therapy continue to respond to sublingual NTG, which suggests that this phenomenon is not true NTG tolerance.

The effect of a nitrate-free interval as a mechanism for avoiding hemodynamic attenuation of NTG therapy is reviewed. The results of 4 studies discussed found that intermittent nitrate protocols were not associated with the attenuated hemodynamic effect observed during chronic therapy. Two possible mechanisms for the vasodilatory effects of nitroglycerin are discussed. The first relates to the production of cyclic guanosine monophosphate in the smooth muscle cells of arteries and veins; the second to the synthesis of prostaglandin I_2 by vascular endothelial cells. A mechanism by which nitrate receptors could be manipulated to increase vascular responsiveness is theorized, as well as a means by which a nitrate-free interval might avoid the development of hemodynamic attenuation in terms of cellular mechanisms and receptors.

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Long-acting nitrates have been a mainstay in the prophylactic therapy of stable angina pectoris for the past 20 years. They can be administered orally, transmucosally or transcutaneously. Oral preparations are administered every 6 to 12 hours in order to obtain 24-hour prophylaxis. Transmucosal preparations are inserted into the buccal space every 4 to 5 hours only during the patient's waking hours to avoid the possibility of aspiration during sleep. Transcutaneous delivery of nitroglycerin (NTG) can be accomplished by application of 2% NTG ointment every 4 to 6 hours. More recently, transdermal delivery systems have been developed that deliver NTG continuously for 24 hours. Two recently published clinical studies have raised considerable controversy regarding the efficacy of long-acting nitrates, in general, and the new transdermal delivery systems, in particular.

This article will (1) present data that emphasize the importance of dose titration in individual patients, including those from our own recent study of the crossover from intravenous to transdermal nitroglycerin in patients with unstable angina, (2) review briefly several major studies on the development of hemodynamic attenuation (tolerance) during long-term nitrate therapy, (3) review 4 recent studies on the avoidance of hemodynamic attenuation by means of a dosing strategy using a nitrate-free interval, (4) discuss the cellular mechanism of NTG's vasodilating action, (5) discuss evidence for a nitrate receptor and (6) speculate on the mechanism by which a nitrate-free interval might avoid the development of hemodynamic attenuation in terms of these cellular mechanisms and vascular receptors.

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Individual Dose Titration

NTG ointment was shown by Reichek et al[1] to result in a significant decrease in systolic arterial pressure, a significant increase in heart rate and a significant increase in exercise duration, 1 and 3 hours after short-term application. After 2 to 3 months of therapy, significant hemodynamic and antiischemic effects could still be demonstrated. In this study, each patient was individually titrated to ensure that an adequate hemodynamic effect was being obtained. The endpoint was a 10% lowering of systolic arterial pressure. A range of doses between 1.5 and 19.6 mg was required to obtain this endpoint in individual patients. This wide range

of doses required to obtain a significant hemodynamic effect emphasizes the limitations inherent in studies that use only a single fixed dose of a vasodilator medication in all patients.

We recently completed a crossover study (from intravenous to transdermal NTG) in patients with unstable angina.[2] This study demonstrated the importance of dose titration in individual patients for both the intravenous and the transdermal routes of administration. Seventeen consecutive patients with unstable angina were treated with intravenous NTG, which was added to any prior calcium or β-blocker therapy. Fifteen of the 17 patients became pain free. Of these 15, 10 patients had catheterization-proven ischemic etiology for their chest pain and no change in other vasoactive medications during crossover from intravenous to transdermal nitroglycerin. All 10 of these patients remained pain free during the first 24 hours after crossover. Seven of 10 remained pain free until hospital discharge. Two patients had a single episode of chest pain after temporary discontinuation or reduction of their transdermal dose. Both became pain free after restarting or restoring their original post-crossover dose. The remaining patient became unstable again, failed to respond to reinstitution of intravenous NTG and underwent urgent coronary bypass surgery.

The crossover protocol was initiated by reducing the infusion rate by 50% and applying a 5 or 10 mg/24 hour transdermal patch. After 30 minutes of observation, if the systolic blood pressure increased by <10%, then the infusion rate was decreased further. If the systolic blood pressure increased by >10%, then another transdermal patch was applied. This sequence was repeated until the infusion was completely turned off. If an episode of chest pain at rest occurred after crossover to transdermal therapy, then an additional 10 mg/24 hour patch was applied.

Five to 40 mg/24 hours of transdermal NTG therapy was required to cross over patients receiving 10 to 200 μg/min of intravenous NTG. Although we have not ruled out the possibility of spontaneous improvement, these results do suggest that crossover to transdermal NTG patches successfully maintains the beneficial antiischemic effects initially obtained with intravenous NTG therapy. These results, like the results of Reichek's study of NTG ointment, further emphasize the need for individual patient titration to establish an effective dose and, in addition, emphasize the wide range and relatively large dose of transdermal NTG required to prevent episodes of pain at rest in patients with unstable angina.

Development of Attenuation or Tolerance

Orally administered isosorbide dinitrate (ISDN) has been shown to increase treadmill exercise duration, decrease systolic blood pressure and increase heart rate in a dose-dependent fashion from 1 to 8 hours after short-term administration.[3] This same study also demonstrated significant attenuation in the systolic blood pressure lowering after 2 weeks of administration of 15 mg of ISDN 4 times a day. In this phase of nitrate therapy, a significant increase in exercise duration was demonstrable only 1 and 2 hours after administration of 15- to 120-mg doses. Attenuation of hemodynamic effects, rather than true nitroglycerin tolerance, may be a preferable term, because in most patients, the authors of this study were describing attenuation of long-term compared with short-term hemodynamic effects.

In order for the definition of true nitrate tolerance to be satisfied, it is also necessary to demonstrate loss of the ability of sublingually administered NTG to increase exercise duration during long-term NTG or ISDN therapy. Such a study was performed by Dalal et al[4] using short- and long-term administration of 30 mg of ISDN. They demonstrated a significant increase in exercise duration 2 hours after a dose of ISDN in the short-term phase of the study. However, 1 week later, after patients had received 30 mg of ISDN 4 times a day, the same dosage resulted in only half of the initial increase in exercise duration previously noted with short-term administration. Sublingual NTG failed to increase exercise duration at a time when significant hemodynamic and antiischemic effects were present. In contrast, 6 hours after an oral dose of ISDN, a time when the antiischemic effects were attenuated, the response to sublingual NTG was intact. This would suggest that patients were not truly tolerant to NTG but only needed a higher NTG blood level for the same antiischemic effect to be obtained.

Leier et al[5] have also showed hemodynamic attenuation in patients receiving oral ISDN therapy for chronic congestive heart failure. They reported significant reductions in pulmonary capillary wedge pressure, mean arterial pressure and pulmonary vascular resistance during the short-term phase and also after 3 months of therapy with 40 mg of ISDN 4 times a day. Attenuation of the arterial pressure-lowering effects was noted during long-term therapy. However, the pulmonary capillary wedge pressure- and pulmonary vascular resistance-lowering effects persisted. Measurements made during exercise revealed that pulmonary capillary wedge pressure, mean pulmonary artery pressure and pulmonary vascular resistance were lowered during both short- and long-term administration of ISDN. Persistence of the preload lowering effects would suggest that the venodilating effects both at rest and during exercise did not attenuate but in fact became even more significant, as evidenced by progressive improvement in exercise duration during the 3 months of long-term administration.

In summary, the results of these studies suggest that the magnitude of the hemodynamic response to nitroglycerin or ISDN diminishes with time; the acute, or first, dose effects far exceed those obtained during long-term therapy. On the other hand, the response of these patients to sublingual NTG persists, suggesting that true NTG tolerance had not developed. In contrast to effects on arterial pressure and systemic vascular resistance, which appear to attenuate markedly, effects on pulmonary capillary wedge pressure and pulmonary vascular resistance appear to persist without attenuation into the long-term phase of therapy.

This may well explain the persistent beneficial effects on exercise tolerance in angina and heart failure patients noted by Reichek,[1] Leier[5] and their co-workers, respectively. Other possible mechanisms responsible for NTG's persistent beneficial effects include dilation of intercoronary collateral channels and prevention of coronary vasospasm. These latter mechanisms of action, like the venodilatory actions, may also persist during long-term therapy and thereby explain the continued clinical benefit observed.

After the development of convenient 24-hour transdermal NTG delivery systems, a new wave of studies was carried out to test the efficacy of NTG therapy in angina pectoris and the clinical importance of hemodynamic attenuation. There seems to be no question that the transdermal delivery systems deliver NTG uniformly over 24 hours, much like an intravenous infusion.[6] NTG blood levels can be shown to be directly related to area of skin used for drug delivery. Beneficial hemodynamic effects appeared to be maintained for at least 10 hours after patch application, with some attenuation evident after 24 hours. Venous plasma concentrations using dosages of 5 to 20 mg/24 hours were low, however, compared with blood levels noted previously after 1.6-mg sublingual doses of NTG or 12-mg doses of 2% NTG ointment.[7] Several early clinical studies suggested that long-term beneficial effects could be obtained using relatively small doses in patients with chronic stable angina[8–11] and in patients with chronic congestive heart failure.[12,13]

In contrast, 2 recently published clinical studies raised significant doubts as to the long-term beneficial effects of transdermal NTG in delivery systems and, likewise, the 24-hour duration of action after a single-dose application. Parker and Fung[14] studied the acute effects of doses of transdermal NTG ranging from 15 to 45 mg/24 hours. They found no significant effects on exercise duration at 24 hours after patch doses of 15 or 30 mg/24 hours. Only at a dosage of 45 mg/24 hours were significant antiischemic effects still present 24 hours after patch application. Reichek et al,[15] using a mean transdermal NTG dosage of 25 mg/24 hours in the presence of concomitant therapy with β blockers or calcium-channel blockers in most patients, found significant antianginal effects after 4 and 8 hours, but were unable to find any significant antiischemic effects 24 hours after patch application.

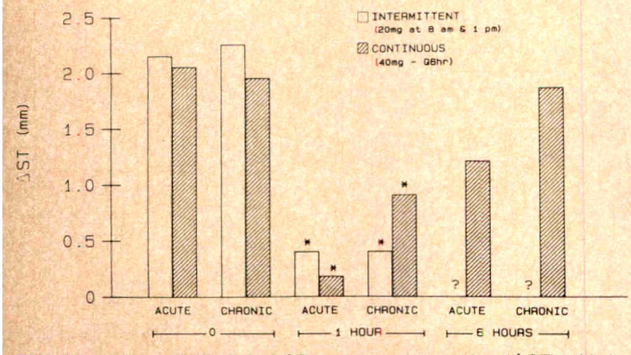

FIGURE 1. Exercise-induced ST-segment depression (ΔST) with intermittent compared with continuous oral isosorbide dinitrate (ISDN) therapy before (time 0) and 1 and 6 hours after dosing. Intermittent therapy consisted of 20 mg of ISDN administered at 8 A.M. and 1 P.M., while continuous therapy consisted of 40 mg of ISDN every 6 hours. Adapted from Rudolph.[17]

In summary, NTG tolerance, or more properly, hemodynamic attenuation, develops with all forms of NTG and ISDN preparations. Attenuation of the arterial dilating effects appears to be more marked than attenuation of the venodilating effects. It remains uncertain whether antianginal effects will follow the venodilating effects. It also remains to be demonstrated whether significant attenuation develops with the direct coronary artery dilating, intercoronary collateral channel dilating or vasospasm-preventing effects. Long-term administration of ISDN to patients with congestive heart failure results in improved exercise tolerance during long-term therapy. Therefore, at least in that patient population, clinical efficacy would appear to follow the persistent venodilating, or preload lowering, effects.

Several investigators have questioned whether continous delivery of NTG, especially at relatively small doses, may actually *promote* the development of hemodynamic attenuation. The quantity of drug delivered could be increased by using larger surface areas of skin (i.e., larger doses). Likewise, "flux enhancers" could be used to facilitate transfer of drug through the skin. It might be possible to prolong the action of the drug by slowing its metabolism. Lastly, the drug action might be potentiated by increasing the number or efficiency of drug binding sites (vide infra). Whether or not increased drug delivery alone will overcome the attenuation of hemodynamic effects noted during long-term nitrate therapy remains controversial and is one of the major goals of an ongoing multicenter trial sponsored by all 3 patch manufacturers. On the other hand, Jansen et al[16] have suggested that larger doses may in fact *increase* the development of hemodynamic attenuation.

A Nitrate-Free Interval

Rudolph et al[17] were the first to suggest that a nitrate-free interval might provide a mechanism for avoiding the development of hemodynamic and antiischemic attenuation. They demonstrated the development of "tolerance" to both the arterial and antiischemic effects of ISDN when 40-mg doses were administered 4 times a day for 2 weeks in a double-blind, placebo-controlled, crossover study. They first tested the response to sublingual NTG, 0.8 mg, in 10 patients during the short-term phase and then again after 2 weeks of long-term administration of ISDN. Sublingual NTG resulted in an 87% decrease in exercise-induced ST depression from 1.20 to 0.15 mm ($p<0.01$), and a 53% decrease from 1.90 to 0.90 mm, ($p<0.01$) during short- and long-term administration of ISDN, respectively. Eleven patients received 40 mg of ISDN every 6 hours for 2 weeks, a regimen that would result in relatively constant ISDN blood levels, and could therefore be considered continuous therapy. These investigators noted a decrease in exercise-in-

duced ST depression from 2.05 to 0.18 mm ($p < 0.01$) 1 hour after a 40-mg dose and from 2.35 to 1.20 mm ($p < 0.01$) 6 hours after a dose during the short-term phase (Fig. 1). In contrast, after long-term administration, ST-segment depression at the same workload decreased only from 1.95 to 1.65 mm (difference not significant) 1 hour after a dose and from 2.05 to 1.85 mm (difference not significant) 6 hours after a dose. Believing that a nitrate-free interval or a smaller dose would limit the development of tolerance, Rudolph et al administered ISDN intermittently, with a dose of 20 mg given at 8 A.M. and 1 P.M., leaving a nitrate-free interval at night. They administered this intermittent therapy to 10 patients for 28 days and found no attenuation of the antiischemic effects they noted previously. In these patients receiving intermittent therapy, exercise-induced ST depression decreased from 2.15 to 0.40 mm ($p < 0.01$), and from 2.25 to 0.40 mm ($p < 0.01$) during short- and long-term therapy, respectively. Thus, for the first time, the development of hemodynamic attenuation after long-term administration of a long-acting nitrate preparation was shown to be avoided by intermittent dosing.

At the 1984 American Heart Association Meeting, 3 presentations dealt with the development of nitrate tolerance and its dependence on dosing strategy. Silber et al,[18] in a double-blind, placebo-controlled trial, compared intermittent therapy, consisting of 80 mg of oral long-acting ISDN given once a day, with continuous therapy, consisting of 80 mg of oral long-acting ISDN given 2 times a day, to determine whether intermittent therapy would prevent the development of nitrate tolerance in patients with stable angina pectoris. They measured exercise-induced ST-segment depression and also ejection fraction before and during exercise (using gated blood pool scintigraphy) on the first and fifteenth days of therapy. ST-segment depression was 0.21 ± 0.6 mm after placebo administration, compared with 0.03 ± 0.05 mm on the first day of intermittent therapy and 0.03 ± 0.6 mm on the fifteenth day of intermittent therapy (Fig. 2). Likewise, the exercise ejection fraction, which was 52 ± 8% after placebo, was 67 ± 9% on the first day and 65 ± 11% on the fifteenth day of intermittent therapy. In contrast, with continuous therapy, ST-segment depression was 0.24 ± 0.7 mm after placebo, 0.07 ± 0.07 mm on the first day and 0.13 ± 0.8 mm on the fifteenth day of continuous therapy. The ejection fraction was 52 ± 15% with placebo, 62 ± 13% on the first day of continuous therapy and decreased to 56 ± 12% on the fifteenth day of continuous therapy. Thus, after 15 days of continuous oral therapy with long-acting ISDN, both the ST-segment depression induced by exercise and the ejection fraction response to exercise were returning toward control values. Although 40 to 65% of the initial improvement remained, neither variable was significantly different from control after 2 weeks of continuous nitrate therapy.

Parker and Fung[19] also studied the role of alternative dosing strategies in the development of nitrate tolerance by comparing intermittent buccal NTG therapy with continuous ISDN therapy. This was a double-blind, placebo-controlled study. The buccal preparation was administered 3 times a day, in 3 mg doses at 7 A.M. and 12 and 5 P.M., with no drug given during the night. Since the last buccal tablet was removed at 10 P.M., this therapy could be considered intermittent. In contrast, oral ISDN was given continuously with 30-mg doses administered at 7 A.M. and 12, 5 and 11 P.M. These investigators reported exercise duration after placebo and then after the first and fifteenth days of either buccal or oral therapy.

Intermittent therapy with the buccal preparation resulted in significant increases in exercise time 1, 3 and 5 hours after drug administration on both the first and fifteenth days of therapy (Fig. 3). In contrast, continuous therapy with oral ISDN resulted in significant increases in treadmill walking times at 1, 3 and 5 hours after a dose only on the first day of therapy. On the fifteenth day, the increase in exercise time was significantly different from placebo only 1 hour after a dose. Exercise times 3 and 5 hours after a dose were not significantly different from those measured after placebo. Thus, as with the 2 previously discussed stud-

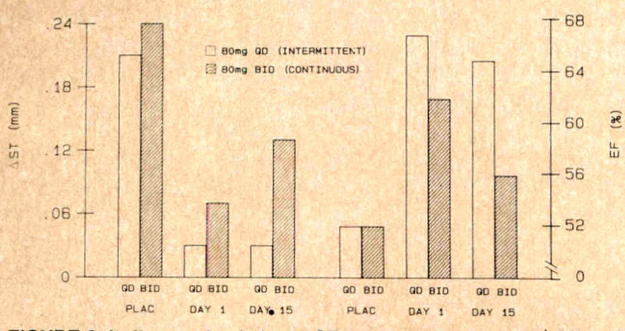

FIGURE 2. Left, exercise-induced ST-segment depression (ΔST) and **right,** ejection fraction response (%) with intermittent compared with continuous oral long-acting isosorbide dinitrate (ISDN) therapy. Intermittent therapy consisted of 80 mg of long-acting ISDN administered once daily, while continuous therapy consisted of 80 mg of long-acting ISDN administered every 12 hours. Data are presented after placebo and 1 and 15 days after institution of ISDN therapy. Adapted from Silber et al.[18]

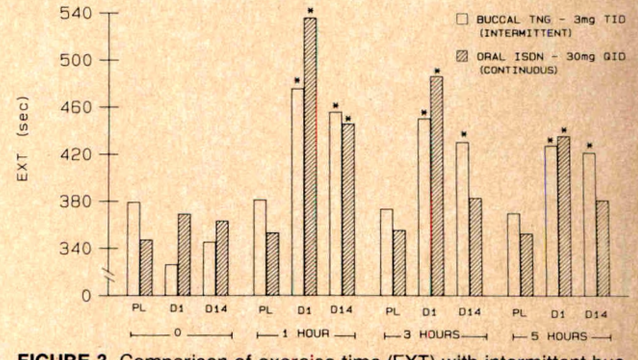

FIGURE 3. Comparison of exercise time (EXT) with intermittent buccal nitroglycerin (TNG) and with oral continuous isosorbide dinitrate (ISDN). TNG therapy was administered as 3 mg 3 times a day at 7 A.M. and 12 and 5 P.M. ISDN was administered as 30 mg 4 times a day at 7 A.M. and 12, 5 and 11 P.M. Data are reported after placebo and 1, 3 and 5 hours after dosing on day 1 and day 14 of therapy. Adapted from Parker and Fung.[19]

ies, these investigators also found that continuous therapy with oral ISDN resulted in the development of "tolerance" (attenuation of hemodynamic effects) within 15 days of initiating therapy. In contrast, when buccal NTG was administered intermittently, no significant tolerance was noted; the beneficial effects on the fifteenth day matched those observed initially on the first day of therapy.

Lastly, Reichek et al[20] compared intermittent therapy with buccal NTG (mean dose 2.8 mg) administered every 4 to 5 hours while the patient was awake with continuous delivery of NTG accomplished by means of transdermal patches. The study was also double blind and placebo controlled. Six patients first received sublingual NTG to test their NTG responsiveness (mean dose 0.38 mg). Before any nitrate therapy, sublingual NTG resulted in a 127-second increase in exercise time; 24½ hours after a transdermal dose, a 99-second increase was noted, and after 24½ hours of buccal NTG therapy, a 116-second increase in exercise time was noted. This study compared exercise times at 0, 1, 4, 6, 10 and 24 hours for intermittent and continuous administration of NTG. Exercise time increased from a control of 271 seconds to 340 to 407 seconds with intermittent buccal therapy across the entire 24-hour period (Fig. 4). In contrast, with continuous transdermal therapy (mean dose 19.2 mg/24 hours) exercise time increased from a control of 262 seconds to 352 to 356 seconds 1 to 6 hours after patch application. However, 10 hours after patch application, exercise time had decreased to 317 seconds, and after 24 hours to 262 seconds, which was identical to the control exercise time. The exercise durations at these latter 2 time points were significantly shorter than the exercise duration noted with intermittent buccal therapy. Again, as in the study by Parker and Fung,[19] since buccal nitroglycerin was not administered during the night, a nitrate-free interval was created.

Mechanisms of Vasodilating Action of Nitroglycerin

The mechanisms of NTG's vasodilating action are thought to be related to the production of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of arteries and veins[21] or to prostaglandin I_2 synthesis by vascular endothelial cells.[22] Axelsson and Andersson[21] examined the development of tolerance to NTG's vasodilating action induced in vivo in rats. They administered 15 mg/kg of nitroglycerin by subcutaneous injection, 3 times a day for 3 consecutive days. Effects on segments of aorta were then tested in vitro, as measured by the cGMP generated. Activity of guanylate cyclase, the enzyme that regulates cGMP production, was also investigated. The relaxation response to NTG in norepinephrine-contracted aortic tissue, obtained from animals pretreated with 3 days of subcutaneous nitroglycerin, was reduced 75% compared with untreated control rats. The ability of NTG to increase cGMP production was reduced by 55%, and the activity of guanylate cyclase when stimulated by nitroprusside was also found to be reduced by 75% in aortic homegenates from nitroglycerin-pretreated animals. cGMP phosphodiesterase, an enzyme that breaks down cGMP, was also shown to have increased activity in nitroglycerin-pretreated rats. These results strongly support the role of cGMP as the primary mediator in nitroglycerin-induced vascular smooth muscle relaxation, and furthermore suggest that nitroglycerin tolerance (attenuation) could be explained by reduced rates of formation and increased rates of breakdown of cGMP.

Trimarco et al[22] studied the role of prostaglandins in the vasodilating action of NTG on the coronary vascular bed of dogs. They demonstrated that inhibition of prostaglandin synthesis by indomethacin or naproxen reduced the coronary hemodynamic response to NTG infusion. They concluded that NTG exerted both a direct effect, which was responsible for the rapid initial decrease in coronary vascular resistance that they observed and that was most likely mediated by activation of guanylate cyclase, as well as an indirect effect, which accounted for persistence of the reduction in vascular resistence and which was mediated through the release of prostaglandins from the endothelial wall.

Finally, Horowitz et al[23] described a mechanism by which nitrate receptors could be manipulated to increase vascular responsiveness to NTG administration. They studied the potentiation of the cardiovascular effects of NTG by the sulfhydryl donor N-acetyl-cysteine in patients in the catheterization laboratory. They suggested that activation of guanylate cyclase by a series of enzymatic reactions was modulated by the availability of reduced sulfhydryl groups. Cysteine had previously been demonstrated in vitro to be effective in potentiating guanylate cyclase activation by NTG. In order to determine whether the hemodynamic responsiveness of NTG might be modulated by sulfhydryl availability, dose-response curves for intravenous NTG, in terms of lowering of mean arterial pressure and pulmonary capillary wedge pressure, were obtained in 10 patients during diagnostic cardiac catheterizations. Intravenous infusion of NTG was then repeated 10 minutes after intravenous administration of 100 mg/kg of N-acetylcysteine. While N-acetylcysteine itself induced no significant hemodynamic effect, after N-acetylcysteine pretreatment, a

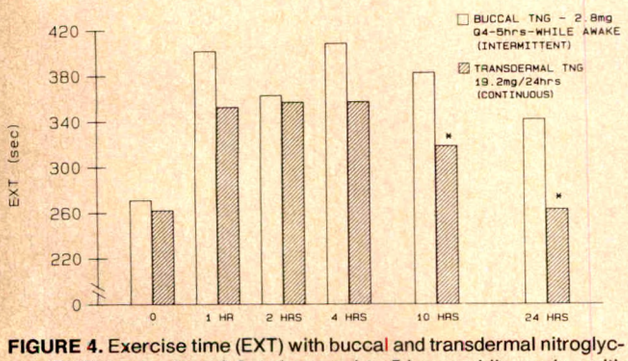

FIGURE 4. Exercise time (EXT) with buccal and transdermal nitroglycerin (TNG) (mean dose 2.8 mg) every 4 to 5 hours while awake, with continuous therapy with transdermal TNG (mean dose 19.2 mg/24 hours). Data are presented before (0) and 1, 2, 4, 10 and 24 hours after initiation of therapy. Adapted from Reichek et al.[20]

significant reduction (64%) in the NTG infusion rate was required to induce a 10% decrease in mean arterial pressure, and likewise, the infusion rate required to induce a 30% reduction in pulmonary capillary wedge pressure was also lowered by 52%. In control patients not receiving N-acetylcysteine, there was no significant difference in NTG responsiveness between 2 infusions of NTG separated by the same time interval. These investigators concluded that N-acetylcysteine potentiated the vasodilator effects of NTG in man and suggested, therefore, that sulfhydryl availability or the redux state of "NTG receptors" may be determinants of in vivo responsiveness to NTG. These data might also suggest a possible mechanism for enhancing NTG's effectiveness as a vasodilator and thereby possibly overcoming the development of NTG tolerance.

Whether the results from the studies of Axelsson and Andersson and Horowitz et al can be related to the mechanism(s) by which a nitrate-free interval avoids the development of tolerance or hemodynamic attenuation remains uncertain. We might conclude that although not structurally identified, functional nitrate receptors bind NTG, activate guanylate cyclase and thereby stimulate the generation of cGMP, which mediates vascular smooth muscle relaxation. In the presence of continuous nitrate therapy, these nitrate receptors might become oxidized, and thereby have lower affinity for NTG binding. These sulfhydryl groups could be restored to their reduced form and thereby NTG responsiveness also restored, either by removal of NTG from the receptor or by exogenous administration of a sulfhydryl donor, such as cysteine. A nitrate-free interval, by allowing blood levels of NTG to fall to near zero, might result in spontaneous release of NTG or its less active dinitrate and mononitrate metabolites from the receptors. Likewise, spontaneous reduction of oxidized receptors might also act to restore NTG's vasodilating efficacy. It is uncertain at this time what minimal duration (e.g., 1 to 12 hours) of a nitrate-free interval would be required to restore full receptor activity.

In summary, the data reviewed would suggest that clinically significant hemodynamic attenuation occurs with all forms of long-term nitrate therapy when the therapy is administered continuously. Whether hemodynamic attenuation can be overcome, and thereby the beneficial effects of nitrates in the long-term treatment of angina pectoris maintained, by higher doses administered continuously remains uncertain and awaits the results of the currently ongoing multicenter trial of transdermal NTG. It seems equally likely that a nitrate-free interval, obtained, for example, by interrupting NTG administration during the night, might provide a means of avoiding the development of nitrate tolerance. For transdermal NTG therapy, this would mean taking the patch off at bedtime and applying a new patch in the morning. For oral, buccal and ointment preparations, this could mean omitting the last dose administered at the end of the day. Whether it will be necessary to administer another vasodilator, such as a calcium-channel blocker, during this nitrate-free period to provide prophylaxis against episodes of silent or clinically apparent ischemia during the nitrate-free interval remains to be elucidated.

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Discussion

Dr. Stephen Scheidt (New York, New York): This morning we heard presentations dealing with all aspects of angina and ischemia—from pathophysiology to treatments to study modalities. I would like to start this discussion by raising some issues about the basic factors involved in assessing patients with angina and developing protocols for antianginal medications. First, we have a major problem with patient selection. What kinds of patients have angina? What kinds of patients have angina in the real world? What kinds of patients have angina in tertiary care institutions? What kinds of patients have angina in studies? I don't think anyone doubts that most of the published results are true—that a certain investigator studies a certain group of patients and gets a certain result. Yet we all know from long experience that the selection of the study group has an enormous bearing on the results obtained. The ability to generalize, or lack thereof, from one group of patients to another is of enormous importance. Everybody participating in this discussion has been involved in drug trials. The patients who join drug trials are, I think, different from the general population, sometimes subtly, sometimes obviously, and I'd like to discuss, first of all, the general issue of differences between patient populations. Then, I'd like to discuss how the kinds of patients who have been studied so far may have a bearing upon the kinds of results that have been reported, particularly in the area of transdermal nitroglycerin.

The second issue, an enormous Pandora's box that has been opened by some during this symposium, is the type of angina present in the patient group selected for study. If we are to fully believe what Drs. Selwyn and Shell have told us, indeed there is really much more angina, or rather much more ischemia, in patients with coronary artery disease than we have been aware of until now. It seems, if you believe Dr. Ganz, that a very large proportion of people, at least those who are studied at the Brigham and Cedars-Sinai hospitals, have unstable angina, unstable ischemia. This question then arises: Are those patients properly represented in the studies that have been done to date with nitroglycerin or other antianginal preparations?

Furthermore, there were a number of issues that arose in Dr. Weber's presentation in terms of the diagnosis of coronary disease. Are there many false-positives in the patients who have been selected? Is it necessary to do a cardiac catheterization in everyone? Is it necessary to look for spasm in everyone? Do we need to look for platelet aggregates or activated forms of platelets in everyone? Do we need, in some way, to look at Folts'[1] types of cyclical changes in coronary flow in everyone to be sure we're studying the right group of patients? Do we need to do echocardiograms in everyone to rule out mitral valve prolapse—because otherwise we may be getting false-positive ST-segment deviations when you do Shell- or Selwyn-type Holters*? There are many questions as to how a proper group of patients with a proper and representative type of angina syndrome is selected for study.

We will want to talk about patient selection and angina selection, and then we will need to discuss test selection. Just what is the proper way to evaluate the efficacy of any antianginal preparation, particularly nitroglycerin? The Food and Drug Administration believes that one needs objective measurements, and of course one does. In this regard, exercise stress testing to submaximal levels has been chosen in the large, multicenter nitroglycerin patch trial that is currently underway. On the other hand, there are many questions as to whether that is the proper methodology for evaluating antianginal efficacy. Holter monitoring, because it's available and because many people are working with it, is another possibility, but is this the right method to use? What sort of work needs to be done in the future? Are there other aspects of study design that need to be taken into account? So, to begin, let me pose the first question to Dr. Weber. How about the question of stress testing for evaluation of angina?

Exercise Tolerance Testing for Evaluation of Antianginal Agents

Dr. Jan R. Weber (Philadelphia, Pennsylvania): Most of the studies, as you mentioned, have utilized stress testing in some way, particularly with regard to the transdermal nitroglycerin preparation. Stress testing on multiple occasions with each patient serving as his or her own control has been used as the standard method. This invariably requires that there be a period of time during which the patient is exercised repeatedly on either no medication or on a stable regimen of medications to determine a baseline level. There is also the matter of the so-called training effect. The training effect may have 2 components: actual physical training, in the sense that exercise performance is improved, and a learning factor—patients tend to learn how to walk on the treadmill over time, they become more efficient and are therefore capable of improving their exercise time, even though there are no significant changes in physiologic parameters that can be measured. So first you must establish an adequate baseline; then it's simply a matter of adding medication or adding placebo to determine whether the response changes.

Dr. Scheidt: Regarding training effect, could part of that be familiarity—less mental stress, less platelet aggregation, less coronary vasospasm? Is that conceivable, Drs. Selwyn and Shell?

Dr. Andrew Selwyn (Boston, Massachusetts): No one knows the answer to that. It is known that in a high proportion of patients with angina, you can standardize exercise tests if you take an enormous amount of trouble, as shown in John Parker's work. It is a reproducible test, but whether you use it exclusively for diagnosis or whether you extend its application for assessing treatment as well is, I think, the central point of your argument. I don't think there is any doubt that it can be standardized.

* For the purposes of this discussion, the term Holter is used to connote 24-hour ambulatory electrocardiographic monitoring. The 2 terms may appear interchangeably.

Dr. Scheidt: How many stress tests do you need for standardization? Dr. Parker, you're the expert on that.

Dr. John Parker (Kingston, Ontario, Canada): The majority of the patients that we study have had 6 or 8 tests. I think that numerous tests are necessary for standardization. It can't be done with 2 or 3 tests. Many of us who are involved in this type of research have a stable of patients, many of whom have been used in multiple studies and thus have standardized stress tests. With a new patient, I would very seldom enroll him in a study in which we are looking at the endpoint of an exercise test unless we could demonstrate that he has reproducible findings within fairly narrow ranges on 4 or 5 different exercise tests.

Dr. Scheidt: Let me immediately point out that it is rare, at least in the transdermal nitroglycerin studies, to see a randomized, double-blind exercise tolerance study that has been standardized with 4 or 5 tests. In most cases, the protocols call for 2 tests with exercise endpoint reproducibility within 10 to 20%. I don't know of any study protocols that have more than 3 tests. So this criterion would not be met in most of the published trials.

Dr. William E. Shell (Los Angeles, California): True, except with those investigators that have a history of doing long-term anginal studies, because by definition their patients have been already trained and standardized. This fact may explain the differences in results between exercise studies.

Dr. Scheidt: Absolutely.

Dr. Shell: If you take a group of patients that have been well trained, they are by definition very stable anginal patients. They can go through a washout phase without jeopardizing their health or precipitating myocardial infarction. These patients are probably a pure cohort of demand-induced angina. It is important to keep that in mind.

Dr. Scheidt: From the tone of your voice, I infer that you think that's probably not the best group of patients to use.

Dr. Shell: Actually, it depends on the agent you're studying. If you're looking at an agent whose major effect is on demand, for example, β blockers that reduce heart rate at any workload, then it may be the ideal study approach. But if you're looking at an agent whose major effect is on the dynamic nature of coronary tone, it may not be the right test. So I think it depends on the agent and on the circumstances. I think exercise testing is a very valuable way of assessing demand-induced angina. The question is whether that's the way to study all antianginal agents and all antiischemic agents.

Dr. Weber: I agree. I think we still have to look at the issue of whether exercise testing is really the appropriate way of assessing the efficacy of these medications. This question hasn't been totally resolved, at least not in my mind. Perhaps much of the data we hope to see from Drs. Shell and Selwyn with regard to Holter monitoring will be useful to us in clarifying the situation. I don't know yet which is the correct method, but I still have some doubts as to whether exercise testing per se is really the appropriate way of assessing these medications.

Dr. William H. Frishman (Bronx, New York): I would like to pose the question somewhat differently. Should a drug that has proven antianginal efficacy, that is, has been shown to reduce the frequency and severity of angina attacks, but which for some reason cannot be shown to improve exercise tolerance, still be available to physicians in practice?

Dr. Weber: I definitely think so, because under those circumstances you are really evaluating 2 different things. One is the ability to produce angina. We know that any person put on a treadmill has a limit. Whether you have coronary occlusive disease or not, everybody tires for one reason or another after a period of time. That's the way that treadmill testing was designed. So if a patient has underlying coronary occlusive disease, it comes as no surprise that regardless of medications, patients will invariably be pushed to the point where angina occurs. But that's really not what happens in their daily living situation. When people are going about their life's work, it's most uncommon for people to try to push themselves to the maximum. So when the angina threshold in these individuals is not exceeded and angina is reduced clinically during their activities of daily living, I think that that is a reasonable endpoint and reasonable goal of antianginal therapy. I don't think that anybody expects all of our patients to be totally free of angina for the rest of their lives once we get them on the ideal medication regimen.

> ***". . . I still have some doubts as to whether exercise testing per se is really the appropriate way of assessing antianginal medications."***
>
> ***—JAN R. WEBER***

Dr. Frishman: Because the FDA still mandates that an antianginal compound be shown to improve exercise tolerance before approval, and I just want to reiterate how difficult it is sometimes to show improvements in exercise tolerance owing to all the variables. One day a patient may go 5 minutes further, and on another day on the same dose go 1 minute further, while at both times the antianginal effects of the drug are consistent.

Dr. Weber: Yes, and it happens not only in cardiac patients, but those of us who are runners know that one day when you go out for a jog through the park, you will feel exquisitely good and have very good times, and the next day you'll run very slowly and feel like a slug, even though there's really nothing that you can put your finger on that's been particularly altered. This clearly happens with patients in the exercise types of protocols that have been designed.

Dr. Shell: I think we have to begin designing trials that are more analogous to the way practicing physicians are using the antianginal agents. It's really not a question of whether nitrates extend exercise tolerance in somebody with mild angina when used as monotherapy. The question is: How does one change the incidence, duration and magnitude of ischemic events in patients with various kinds of disease?

Characterization of Ischemic Disease

Dr. Scheidt: Would anybody care to estimate the incidence of supply- versus demand-induced angina? After all, what we really want is results that can be generalized to the real world and to the general population with angina. That may not be possible. It may be necessary to subdivide patients in the real world, but until now, there's been relatively

little of that. A patient with angina is any patient with angina, unless he clearly has unstable or Prinzmetal's angina. Most patients are handled as some unknown mixture. Most of them do have atherosclerotic disease, so there is an element of a demand problem. We would probably all agree that there may be some element of coronary vasospasm as well. But would you care to give an opinion as to whether there is a great deal more in the way of supply problems in the general angina population than we have heretofore been considering and that our current studies are designed to look for?

Dr. Selwyn: I don't think we have any idea at the present time. To categorize patients with angina into purely 1 group or another seems to have no basis in fact or in usefulness. If you take all of the patients with consistently reproducible positive exercise tests that we have studied, over 90% of those that you might like to call purely demand-induced angina are having asymptomatic ischemic events and symptomatic out-of-hospital ischemia without any apparent increase in demand at all. So, as far as we are concerned, the general characteristic of the disease is that of ischemia under mixed circumstances, and it is exceptionally rare to find the Prinzmetal's angina patient with normal coronaries at one end of the range or the purely exercise-induced angina patient at the other end.

When we started looking into the area of silent ischemia, we found that the majority, rather than the minority, of people that we monitor have asymptomatic ischemic characteristics on Holter tapes out of hospital. If you look at the ischemic events, Holters are probably much more objective than the patient's reported symptoms. But the fact is that they still can't tell you what events are taking place in the proximal epicardial coronary arteries. Holters cannot measure what catecholamines have done to the myocardium apart from the effect on heart rate. They don't include information about tension development at the same heart rate, which might alter as well. In other words, the factors that contribute to increased demand are many and the increases necessary to cause ischemia can be very subtle, perhaps an increase of 5 or 7 beats/min, so demand may fluctuate without detection. The question of coronary tone is even more difficult to identify. The point is that at the present there are 2 objective ways—exercise testing and Holter monitoring—of looking at the activity of the disease and these are mutually inclusive.

Dr. Scheidt: Now I'm a little puzzled. Five or 6 years ago, when Maseri's group burst on the scene with the various descriptions of spasm, a number of studies were done evaluating gross vasospasm. The one that comes to mind is the ergonovine study by Bertrand[2] in Toronto. In this study, I believe that patients who clinically only had exercise-induced angina had about a 5% incidence of positive ergonovine tests, and patients with almost exclusively angina at rest had about a 40% incidence of gross vasospasm at catheterization. Patients with rest and exercise angina had about a 15% incidence of vasospasm. This is much less than a majority. Yet you and Dr. Shell, and the several other investigators that you both cited, show much more than the majority of patients with some sort of asymptomatic, nondemand-related ischemia. How do you put that together?

Dr. Selwyn: You have just made 2 assumptions. First, that nondemand-induced angina is the result of coronary vasospasm, and second, that a positive response to ergonovine has something to do with the real activity of the disease that affects people out of hospital.

Dr. Scheidt: All right. If it is not because of vasospasm, is it because of platelet aggregates, or is it because erogonovine has a great many false-negatives?

Dr. Selwyn: No, I think we have to say at the present time that we don't know. It is food for research. Currently, the detailed sequence of mechanisms that affect each patient at any 1 time in their disease cannot be dissected out. Of course, we do have some general ideas regarding the pathophysiology of the disease. For example, we know that the majority of patients who present with angina, positive exercise tests and angiographic stenoses have those stenoses underestimated at coronary arteriography. The reduction in cross-sectional area is probably greater than we think. The second thing we know is that the majority of these people will have a great enough reduction in cross-sectional area to produce a pressure gradient, so that the poststenotic pressure is decreased, very often to the level that the subendocardium becomes pressure driven and is therefore jeopardized. And the third thing we know is that superimposed on that particular narrowing the vessel is capable of constricting and relaxing. So there you have the set-up with 2 or 3 reasons why supply might be badly upset during an ischemic episode. Moreover, there's a lot of basic research that is perhaps more convincing than the clinical work. This research suggests that when atherosclerotic lesions have very active cellular content and various growth factors and hormones are secreted locally, these vessels can have an abnormal increase in tone. My colleague, Peter Ganz, has done wonderful work in our catheterization lab showing that the endothelial-dependent relaxation of these vessels in humans is destroyed. So there is evidence of endothelial instability. All of these mechanisms are possible contributory factors and may be present in variable proportion, but you can't dissect them out in an individual using current types of monitoring.

Symptomatic Versus Asymptomatic Disease

Dr. Parker: I would like to ask either Dr. Shell or Dr. Selwyn if there is any relation between silent ischemia and the severity of angina? Do patients develop it in 1 minute on the treadmill? Ten minutes?

Dr. Selwyn: The relation to the treadmill is interesting. In the 2,000 episodes we looked at in London and the 1,000 in Boston, there is no difference in the characteristics between the painful and the painless episodes. They're just as severe, just as prolonged, and they have the same heart rate distribution a minute before. We couldn't find any convincing difference. There were minor differences, with very big overlap. We concluded that there doesn't appear to be any great difference in the characteristics between symptomatic and asymptomatic ischemia. Now in the exercise test, there is a difference. Steven Campbell, who is a cardiologist now working with us, has looked at our last 40 patients. He has found a very strong relation between the levels of positive response on the exercise test and the amount of ischemia occurring out of hospital. It appears to be, with overlap again, that patients with positive exercise tests at low workloads have more ischemia out of hospital.

Dr. Parker: In selecting patients for angina studies, we tend to have patients who will get pain within stage II or early stage III of the Bruce protocol, because once you get into 9 or 10 minutes of exercise, it's hard to show a drug effect. People just tire out. Patients who develop pain at stage II or III have fairly severe disease. Would the subset that we are selecting for our drug protocol tend to have a higher incidence of silent ischemia?

Dr. Selwyn: Yes, that's right. At stage I and II, and early stage III, they will be having anything from 4 to 15 episodes of asymptomatic ischemia a day out of hospital. At the higher stages, once they can exercise for 12 minutes, they have much fewer episodes out of hospital.

Dr. Scheidt: This is a very important point, because with the National Institutes of Health exercise protocol reported on 10 years ago by Redwood et al,[3] it was suggested that the way to select patients for angina trials is to take people who get angina between 3 and 6 minutes—this illustrates what Dr. Parker just said.

Dr. Parker: Well, that's a little different, because they were modifying the workload so that the angina would come in 6 minutes. You could have anyone from class I to class IV

Dr. Selwyn: We were using, of course, the standard Bruce protocol. But we were asking the question of why the low positive exercise test carries such a bad prognosis. And the answer appears to be, at least in Steven Campbell's work, that they are having much more ischemia out of hospital.

Dr. John T. Flaherty (Baltimore, Maryland): Dr. Shell, did I understand you to say that in your open-label trial you found a dissociation in the response of the silent ischemic episodes and the symptomatic exercise-induced episodes to transdermal nitroglycerin therapy; that the transdermal therapy worked very well for suppressing silent ischemia but not so well for suppressing symptomatic exercise-induced ischemia?

Dr. Shell: We haven't studied that systematically. I can only tell you that in patients who have exercise-induced ischemic events, it doesn't appear that we are able to abolish these events completely. People will go on having exercise-induced ischemia, and they'll take nitroglycerin for it. A study in which silent ischemic episodes are abolished and exercise testing is subsequently performed has not been done, and it badly needs to be. In addition, there are several other points to be made. Going back to Dr. Scheidt's question regarding the conditions in which nitrates are likely to work, I think that 3, 4 or 5 years from now we're going to find that nitrates in all dosage forms that provide sufficient blood levels, both transdermal and oral, are going to be useful for the treatment of these spontaneous events, whether vasospastic or demand in origin. Currently, we're just beginning to define the technology that's going to allow us to do that. My guess is that dosages will be pushed to 20, 40 and 60 mg of transdermal nitrates for exercise-induced ischemia, and there will be some effect. There'll be a 10 or 20% increase. It may disappear in 24 hours, but the incidence of these silent episodes will go down dramatically. That's my prediction. Now, is this significant? To be able to answer that, it's quite clear there are 2 pieces of information missing. First, are these silent events prognostically significant? Is there an increased incidence of these events just before a myocardial infarction? Is there a relation between the total number of ischemic events and subsequent myocardial infarction and sudden death? I think Dr. Selwyn has some preliminary data suggesting there is. Second, if you abolish silent ischemic events through treatment, do you change the relation? This is not known at the current time. But if you're planning trials that will be completed 6 months from now, a year from now or 3 years from now, you'd better have that information. Otherwise you're going to get into this dissociation problem.

Dr. Scheidt: It was mentioned here that 3 out of 80 or so patients with silent ischemic episodes have died in Jansen's[4] trial. That's a rather high number given the findings in the CASS trial,[5] for example. It's hard for me to square what you're saying—first, that there's an enormous amount of asymptomatic ischemia in the population; in fact, almost everybody with chronic stable angina has it, and second, that these episodes are important before a myocardial infarction. After all, the clinical experience of most physicians with a standard, unselected, nontertiary-care group of angina patients is that they don't die at a very great rate. So there seems to be a discrepancy.

Dr. Frishman: Well, they're treated.

Dr. Scheidt: That could well be.

Dr. Selwyn: Also, in the categorization of patients, the CASS study that you just quoted didn't even require exercise testing. Many of the patients had little or no symptoms. You have no idea if they are the patients that we've been talking about around this table. You have no idea if they have any active ischemia whatsoever. I don't think you can group patients and categorize them until you've looked at them individually with respect to symptoms, active ischemia and coronary anatomy. Those factors will tell you whether they are the type of patients that we are talking about. Dr. Parker studies people who reproducibly get ischemia on exercise. He knows physiologically who they are from his standpoint. In the CASS study, I think many of them were never exercised.

Definition of Anginal Populations

Dr. Shell: There is a critical point, though, which is the description of study groups in published reports. It's going to be important that the editors make the authors define their anginal populations. They've got to define the time to a positive exercise test response, both as a mean and standard deviation, and the number of ischemic events at baseline on Holter monitoring. John Parker's group, for example, may have no silent ischemic episodes. He may have selected a cohort of patients who have no silent ischemic episodes, but we don't know that. So I would stress the importance, at least to journal editors, of making the authors define their patient groups. How many previous exercise tests have they had, what are the training phenomena, how many silent episodes do they have? Otherwise, we're never going to sort out any of these issues. We seem to be comparing apples and oranges and grapefruit trees, and we don't know where we are.

Dr. Scheidt: Someone alluded to it earlier, but I want to raise it again. How about a patient's ability to be withdrawn from other antianginal medications? Wouldn't that also define a somewhat different group?

Dr. Selwyn: In the selection of our patients, it's a crucial first issue. If you perform Holter monitoring on usual doses of their antianginal medications, you see very few ischemic events in a large number of the patients. Once you take them off and they use nitroglycerin alone, sublingually, then the patients' responses more closely approximate their natural state. That is very common practice in clinical trials, but many practitioners are not comfortable doing that.

Dr. Shell: Not only that, but the usual washout phases are 2 weeks. This is too long. We're doing a trial with a β blocker right now, and it has a 2-week washout period. It has to be modified, because these patients probably can't go more than 48 hours without their usual antianginal medications. If they do, their frequency of both symptomatic and asymptomatic events begins to increase. They are thus at risk of developing a myocardial infarction during the washout phase.

Dr. Selwyn: We've probably studied more than 300 people over a 6- or 7-year period, and we have never had any adverse events or any troublesome side effects from taking them off drugs. We have explained to patients that they're going to get some recurrence of angina, and when they do, they should use nitroglycerin. We take other precautions as well, but we have never run into trouble doing that.

Dr. Shell: What's the duration of the washout?

Dr. Selwyn: Forty-eight hours. We would never go for a 2-week washout period.

Dr. Scheidt: Dr. Frishman, you have had a lot of experience with this. What do you think?

Dr. Frishman: Yes, we've actually done drug studies requiring drug withdrawal or washout in hundreds of patients through the years. We've had washouts as long as 4 weeks in certain studies. I must say that if you know your patients well and they are informed that they should modify their daily activity and take nitroglycerin whenever they develop chest pain, you can safely use long washout periods.

Dr. Selwyn: All of our complications, including deaths, have occurred months after the Holter monitoring when these patients were back on their usual medical therapy, often with controlled angina pectoris.

Dr. Shell: Once again, though, the point that Dr. Frishman has to understand is that if you have a group of patients that can go 4 weeks on a washout period, you have defined a certain class of patients. It would be very important for you to Holter monitor those patients at the end of the 4-week washout period to determine their incidence of silent ischemia. I would hypothesize that they probably have a very low incidence of spontaneous events.

Dr. Scheidt: So Willie Ganz's tongue-in-cheek comment—that almost everyone has unstable angina—applies to virtually everyone with a strongly positive stress test who has a lot of asymptomatic episodes on a Holter, is on multiple drug therapy and is referred to a tertiary care institution. Is that a fair assessment?

Dr. Selwyn: Moderately positive and strongly positive.

Dr. Shell: I don't use the term unstable angina, because it has certain medical-legal and treatment implications. These patients certainly have unstable ischemia, and I think that term is a fairer characterization. To me, unstable angina means progressive incidence of chest pain with electrocardiographic changes, and I think we ought to restrict the term to that.

I'll tell you 2 interesting anecdotes that will point out another problem, which is that this active phase of ischemia may have a time course to it, a factor that is going to further complicate matters. A lawyer I'm following for recurrent paroxysmal atrial tachycardia comes in and says he's no longer able to jog as far as he used to. I put him on a Holter, and he had 8 or 10 silent events with no chest pain at all—1-, 2- and 3-mm events. I put him on a treadmill and he developed 3 mm of ST-segment depression without pain. I had him catheterized and found he had a 60% proximal left anterior descending lesion with what appeared to be a luminal clot. You could see a blush, but it was not occlusive. He was then placed on transdermal nitrates, β blockade and aspirin. He was followed with Holters for 3 months, and the incidence of his ST-segment events decreased with time. Did he have a healing atherosclerotic lesion?

The second patient was a malpractice lawyer, who in January did 12 minutes on a treadmill with no problems. In February, he noticed a decrease in exercise tolerance and in April he began having episodes of chest pain. At that time, he was found to have alternating ST-segment changes on his resting electrocardiogram, and was admitted to Cedars-Sinai with a diagnosis of unstable angina. He was placed on intravenous nitroglycerin and rapidly cooled down. He was taken to the catheterization lab and found to have a 20% proximal left anterior descending lesion. There was some suggestion of a blush if you looked very closely at the films, so it was assumed that he had ruptured an atherosclerotic plaque. He was placed just on β blockade and sent home. That was on Friday. I saw him in the emergency room on Friday night and again on Saturday night. I put him on the treadmill on Monday. He developed 4 or 5 mm of ST-segment elevation on the treadmill. I put him on transdermal nitro patches in addition to β blockers, and his episodes went away. A week later he did 12 minutes on the treadmill. Then we put him on a Holter, had him stop his transdermal nitrates and within 2 hours his episodes were coming back. What's his disease, and is there a time course? He is currently on transdermal nitrates and β blockers. We'll follow him out to 6 months and then stop his medications, but it's likely that these unstable lesions have a time course. They're not the same week to week.

Dr. Scheidt: That, of course, has been known to be true with Prinzmetal's angina for some time. There are periods of activity followed by periods of inactivity.

Dr. Selwyn: Angina typically exhibits exacerbations and remissions over days, weeks and months.

Dr. Parker: That presents a problem in some of these clinical trials that are too long.

Dr. Selwyn: Yes. They remit spontaneously.

Dr. Flaherty: How do you control for the use of coronary angioplasty or bypass surgery in these populations? There seems to be an underlying assumption that these populations are going to stay untouched by invasive hands throughout this time. At our institution, patients with unstable angina are catheterized, and if the lesions look fixable, they're fixed. Are you studying only nonangioplastiable or nonoperable patients? Are you studying only patients who have too little or too much disease to qualify for surgical intervention?

> ***". . . it's a false aim to try to do any study hoping to find results that can be applied to all patients with a variable disease. I think that as long as investigators are very specific about who they've selected, time and multiple studies will tell whether the information becomes useful in the general [anginal] populations."***
>
> ***—ANDREW P. SELWYN***

Dr. Selwyn: We have exactly the same routines as you do. Most of our patients who have angina or angina equivalents and positive exercise tests have Holter monitoring before they ever come to the catheterization rooms. Then at catheterization, there is usually a diagnostic test, followed by an angioplasty 2 or 3 weeks later. That 3-week gap allows us to make other observations, clinical trials, etc.

Dr. Flaherty: Most of our hospital angioplasties are being done at the same sitting, or the next day at the latest.

Dr. Scheidt: That's all very fine for studies of Holter incidence of ST-segment deviation, but it is not fine for assembling a group of patients for a medium-term drug trial. One has to question whether the patients who are still available for drug trials are different from those of the general population.

Dr. Shell: I'm doing it differently. My position is that as long as I can control people on medical therapy, and they do not have uncontrolled angina, I can therefore follow them. I'm referring for surgery only those that I cannot control medically. So I've developed a cohort of people, up to 35 now, who have not been catheterized, but at least I'm following them long term with Holters.

Dr. Scheidt: But people who are controllable probably fall less into the category of unstable ischemia than the patients we've been talking about. There are obviously gradations here.

Dr. Selwyn: I don't think your aim should be to select a population and then generalize to the entire population of patients with ischemic disease. I think that as long as investigators are very specific about who they've selected, time and multiple studies will tell whether the information becomes useful in the general population. I think it's a false aim to try to do any study hoping to find results that can be applied to all patients with a variable disease. The populations that we and others have chosen are not unreasonable —people with chronic stable angina of different levels of severity and with different reproducibility on exercise tests —but we have carefully defined our populations. Many more studies need to be done and then perhaps we will be able to arrive at more and more general conclusions.

Dr. Scheidt: Dr. Roberts had a comment.

The Ideal Protocol

Dr. William C. Roberts† (Bethesda, Maryland): Yes. Dr. Shell mentioned journal editors in one of his remarks, and you've discussed protocol, patient and physician. I just wondered if Dr. Shell were to develop what he believed to be an ideal protocol to study anginal patients, and then he passed that protocol around to the rest of you gentlemen, how many would come to a general agreement that the protocol developed by Bill Shell was really rational and reasonable, that the number and type of patients were fair and that the physicians chosen were reasonably qualified to do that study? I realize this is a little separate from the purpose of this symposium, but it's obvious to me that there is no agreement in terms of what is ideal. Surgeons, for example, in talking about prosthetic valves, have set up very nicely what is an ideal prosthetic valve, and there's no disagreement on that. But what is an ideal protocol, agreed upon by a number of thoughtful investigators, that editors can accept and the medical community can believe?

Dr. Shell: I think the problem is not ideal protocols, because I agree with you, I don't think ideal protocols can be designed. I think the key issue is that there should be sufficient detail in the description of the study design so that people reading it can come back and reconstruct the study conditions. For example, in the Reichek study that was published in *The American Journal of Cardiology*,[6] one has a great deal of difficulty going back through it to find out who was studied. Who were those patients? How many previous exercise tests had they had? What I am asking for is more details in the method sections of clinical trials, even if they are published as an appendix or kept on file at the journal, so that when you're reading a trial there is a way of discerning who is being studied. But I don't think that you can develop an ideal protocol.

Dr. Roberts: Why can't you develop an ideal protocol? I mean, if you had your druthers, what would be your vision of an absolutely perfect protocol? It seems to me that it would be useful to have such an ideal.

Dr. Shell: We spent 2 years designing a transdermal nitroglycerin protocol for assessing silent ischemia. The problem was that we had insufficient knowledge to design the protocol. We had several questions we couldn't answer. One was this question of day-to-day ambulatory electrocardiogram tape variability; you have to build this into a study design if you're going to get appropriate numbers. Another was not knowing what kind of dosage forms to use. So I think part of the problem is insufficient knowledge of both the medications and the endpoints in the disease to design protocols appropriately. We don't know enough about the nature of the disease processes to design truly valid scientific protocols, and so there is an artificial attempt to put science into something that is in many ways an art.

Dr. Roberts: But Jan Weber was fairly critical of all these factors. I could go away from this discussion thinking it's impossible to do a good study.

Dr. Selwyn: I don't think it's impossible to define ideal goals. The reason why protocols are less than ideal, and the reason for the problems here, is that very often the research question is not sufficiently precise. The research question is frequently pretentious and attempts to generalize the efficacy of a drug for the management of a patient for life, rather than saying, can this drug favorably affect 1, 2 or 3 objective measurements, with the understanding that that's not the whole story. If you wanted the whole story, I don't think it's too hard to say that you need these drugs to control pain and active ischemia, prevent infarction and prolong life. These goals must be approached in steps.

Dr. Roberts: What if you were setting up an ideal protocol just to test the efficacy of transdermal nitroglycerin?

Dr. Selwyn: To do what? What is the research aim?

Dr. Roberts: To relieve overt chest pain, angina.

Dr. Selwyn: Looking at relief of pain has been done. And it falls short because pain is such a subjective symptom and so difficult to assess objectively.

Dr. Roberts: What would be your question, then?

Dr. Selwyn: Well, that's my own bias. We come straight back to the defense that if I passed it around the table, others might not agree, but I think that you have to use what is familiar. This would be first, the full characterization of the patient, as Dr. Shell has said, second, the standardized exercise test, because it is traditional and contains prognostic information and third, the control of all ischemia out of hospital, whether it is symptomatic or asymptomatic.

Dr. Roberts: But you've got to throw out the first 4 or 5 exercise tests before you start on that.

Dr. Shell: Or at least describe them.

Dr. Selwyn: Yes. It's difficult; we accept that.

Dr. Shell: I'd like to back up. I think we've got a fundamental problem. In acute myocardial infarction, we can agree that the endpoint is mortality rate at 1 month and 1 year. I don't think we have developed our thinking in angina pectoris to the point where we can agree on an endpoint. That's what's fundamentally stopping us in the discussion of what is an ideal protocol, or what is an ideal dosage form. I think that we need to begin evolving careful clinical subsets of patients with agreed-upon endpoints. I think John Flaherty's study is a fascinating example of a spectrum of very unstable patients who've been admitted with unstable angina, probably having multiple ischemic events, both silent and symptomatic. In contrast, there is Dr. Parker's group of patients, who are able to participate in studies over many

† Dr. Roberts is Editor-in-Chief of *The American Journal of Cardiology* and was present in the audience of the symposium.

years with extended washout phases and are probably quite stable. Until we have an assessment of those kinds of clinical subsets, and what endpoints may be useful, we cannot resolve the kinds of questions we've been discussing. I think we are going to find that to begin resolving these issues we have to develop multiple marker studies analogous to what we have in myocardial infarction. Then we will need to begin looking at relative dosages in the individual subsets. The original work done in England used 5-mg patches. It may be that that was a totally inadequate dose to deal with a very unstable group of patients. We don't know. We're just beginning to scratch the surface regarding how to do the subsetting.

Dr. Weber: I think the other thing that makes it difficult to define an ideal protocol is that the clock is moving. Five years ago, before Maseri's work in Italy, we weren't really thinking seriously about the role of coronary vasospasm in angina. Now it's a major consideration. Similarly, in recent years, Drs. Selwyn and Shell have developed techniques for completely renovating our entire concept of coronary ischemia.

Dr. Roberts: I am seeking the ideal protocol for 1985. It could change in 1987.

Dr. Shell: I agree with Dr. Selwyn. I think you are going to need to have multiple levels—complete clinical characterization, exercise tolerance, whether it's trained or untrained, as long as it is specified and you know what you're dealing with, the degree and magnitude of ischemia and the number of episodes of chest pain. In this way, the research goals of each trial can be limited. One particular phase can thus be studied, and by the time we're done—1, 3, 7 years from now—we'll be able to say, for example, that β blockade can control exercise-induced ischemia. It can't control, as a hypothesis, spontaneous ischemia. It is effective in this class of patients, but not in that class of patients. Perhaps we'll find that transdermal nitrates in trained individuals have no effect on exercise-induced ischemia, but in untrained individuals it may, or it may have a tremendous effect on spontaneous ischemia. Then, by using multiple endpoints, we can begin to give the clinician some way of quantifying his obvious impression, that, clinically, multiple agents seem to be able to control the disease we call angina pectoris. The clinician is now confused. He doesn't know what endpoint to use. He certainly doesn't use repetitive exercise testing in his office to treat chronic stable angina. I don't know of any clinicians who do that. So the FDA is imposing an endpoint that is really very far away from what the average practitioner is using to assess treated patients. Maybe the FDA is right. Maybe everybody should do an exercise test, put people on antianginal agents and then repeat the exercise test every 3 months. Medical insurance carriers would probably be horrified by that.

Dr. Roberts: Well, not only is the practicing physician confused, but the investigators can't agree, it seems to me.

Dr. Selwyn: No, I don't think there's a major disagreement. I think most people around the table agree that patients should be characterized with a great deal of detail, that the standard exercise test has value and that there is value in looking at the amount of ischemia that's going on out of hospital. All 3 of these factors should move us closer to making the ideal study.

Dr. Roberts: Okay, suppose two of you do separate studies; in 1 study, 70% of the patients with angina have systemic hypertension and 50% of them have healed myocardial infarcts, whereas in the other study only 20% of the patients have systemic hypertension and 10% have healed infarcts. Are we talking about the same group of people?

Dr. Selwyn: That's not the purpose. As Dr. Shell said, if you explain all of the patient characteristics in your methods section in the greatest detail, those people who read your article will extrapolate your findings only to that patient population when they come to practice.

Dr. Shell: One of the problems we've had is that many of the active investigators have been focused on the coronary care unit, and as Dr. Selwyn points out, have not been moving out from the coronary care unit into the real world. That's changing. I don't think the situation is nearly as hopeless as it may seem. I think that the Parker-Reichek articles have crystalized an issue on which people are beginning to focus—attenuation. There are many new criteria that now need to be evaluated. Is there attenuation of nifedipine effects? Is there attenuation with diltiazem? There may be if it's looked at in ways other than exercise testing.

> ***". . . what we need to do over the next several years is expand the work . . . to the whole spectrum of angina patients. We will want to use different endpoints and see how different drugs affect those endpoints."***
>
> ***—STEPHEN SCHEIDT***

Dr. Scheidt: Let me summarize then. I believe that although there seems to be a great deal of disagreement, there is really less than we think. What we have said, and the reason for this discussion, is that most of the data reported up to now has been using only a certain subgroup of angina patients using only a certain type of testing. What I think becomes quite clear, from both the studies that have been done and from our intuition, is that angina is not a single disease. It's not even as simple as vasospasm-versus-supply-versus-demand angina. Angina is a very complex disease syndrome. It probably varies with time in the individual patient; it varies in individual patients according to coronary anatomy and it likely varies in response to therapy. We simply have to characterize what is going on. It is highly unlikely, I think, that any single agent is going to be the best agent for angina as a global disease. Until now, most of the studies have used 1 test and presumed that the test was looking at 1 type of patient. This patient has, in general, been the type of patient who was not unstable, could perform several exercise tests over a good period of time and could have other therapies withdrawn without difficulty. I think that what we need to do over the next several years is expand the work, and certainly that is underway, to the whole spectrum of angina patients. We will want to use different endpoints and see how different drugs affect those endpoints.

Dose and Efficacy

Dr. Scheidt: Let's turn now to a question that has plagued us all: the question of dose. Will the problem of efficacy, or perhaps the problem of development of tolerance or attenuation, whatever the semantics used, be solved or at least partially obviated by changing doses? Dr. Shell, what do you think?

Dr. Shell: I think it's going to be a double-edged sword. I think we're going to uncover a new problem, that of dependence. It will be the same kind of problem that you get into with β blockers—how do you get patients off of them? I think we are going to find that there are patients who will respond to higher doses, and then you'll have a dependence problem.

Dr. Weber: On the other hand, the dependence problem doesn't negate our use of β blockers. We still use them.

Dr. Shell: It's really not a question of whether nitrates extend exercise tolerance in somebody with mild angina when used as monotherapy. The question is: How does one change the incidence, duration and magnitude of ischemic events in patients with various kinds of disease?

Dr. Scheidt: Does anybody think that responsiveness to an additional sublingual nitroglycerin for an attack of pain will be seriously compromised by standard doses, by higher doses or by the highest doses?

Dr. Parker: The data that I have mentioned suggest a normal response to all doses. There is a dose response in blood pressure and exercise tolerance from 15 to 120 mg of isosorbide dinitrate.

"It's really not a question of whether nitrates extend exercise tolerance in somebody with mild angina when used as monotherapy. The question is: How does one change the incidence, duration and magnitude of ischemic events in patients with various kinds of disease?"

—WILLIAM SHELL

Dr. Scheidt: It's been said several times, and certainly Dr. Parker has shown us data, that there really is a problem of attenuation, and it's unrelated to blood levels. On the other hand, let me be a little bit iconoclastic and point out that there are a few studies that indicate that blood levels with a single sublingual nitroglycerin dose are considerably higher than those you reach, for instance, even with substantial doses of transdermal nitroglycerin. Is it possible that there may be a blood level problem at lower doses of transdermal nitroglycerin? After all, with a sublingual nitroglycerin, you get a very rapid rise in nitroglycerin blood levels to more than 3 ng/ml, which is much higher than you get with a 5-, 10- or 15-mg patch.

Dr. Flaherty: We, too, have measured nitroglycerin blood levels, both with patches and with intravenous dosage forms. I always like to remind people that the venous blood levels that one measures are in a sense downstream from the organ of absorption. In other words, the drug, whether it's given transcutaneously or intravenously, sees central veins, arteries and capillaries before it sees the peripheral veins. In the intensive care unit where we already have central venous and arterial catheters, we can simultaneously obtain samples from the right atrium, the radial artery and a peripheral vein. With patch doses in the range of 60 to 100 cm^2 (30 to 50 mg/24 hours) we're obtaining arterial and central venous blood levels as high as 40 mg/ml, but often peripheral venous levels <1 mg/ml. These measurements would seem to confirm that the transdermal patches deliver nitroglycerin in adequate quantities. I've always had an argument with measuring peripheral venous blood levels, because we see patients who are demonstrating significant hemodynamic effects with intravenous nitroglycerin who have a peripheral venous blood level of 0. These patients must be extracting most of the nitroglycerin into pulmonary vascular and peripheral arterial smooth muscle cells and thus, there is not much to spill over into the peripheral venous circulation.

Development of Attenuation

Dr. Shell: I have a question for Dr. Parker regarding your high dose data. Have you done any trials in which you've used 1 patch, seen the development of attenuation and then placed a second patch?

Dr. Parker: The high-dose study was short term, using 1 dose. We did not use a second patch.

Dr. Shell: Because if the question is does the drug work, even your data would suggest that at the end of 24 hours, the high dose works. You raise the biologically significant work. Therefore, the drug is effective. After all, that is the relevant question. With each successive patch do you see this 24-hour effect?

Dr. Frishman: I have a couple of questions, again, going back to basic mechanisms with disulfite formation. It's been stated that if you give nitrates and tolerance develops, patients shouldn't even respond to sublingual nitroglycerin. The response to any nitrate that's given should be blunted at that point, and perhaps that whole theory of disulfite formation causing tolerance is wrong.

Dr. Parker: Unless the rapidly rising nitrate levels act to displace substrates from receptors.

"The isosorbide dinitrate data are very similar to what we see with prazosin, with the initial loss of hemodynamic effect. . . But we can overcome this problem by administering higher doses and long term we can get a sustained effect."

—WILLIAM H. FRISHMAN

Dr. Frishman: Yes. The other thing that I've seen from the blood pressure studies in which we've been involved is that when you use vasodilators, including prazosin, after the first few days of therapy, there is actually a return toward baseline, probably related to hormonal compensations. The point is, however, that although these patients return toward baseline, it doesn't mean that the effect has worn off. We can reinstate the drug's effect by giving larger doses over a period of time and obtain a sustained antihypertensive effect. The difficulty lies in a short-term study. The isosorbide dinitrate data are very similar to what we see with prazosin, with the initial loss of hemodynamic effect. The pressure doesn't go down as much because the body has

made compensations for it. But we can overcome this problem by administering higher doses and in the long term, we can get a sustained effect.

Dr. Shell: Dr. Parker, were your studies done as monotherapy, with only nitrates on board? Are there any data that assess the influence of β blockade on the development of attenuation? Because theoretically it's possible that the β blockade could attenuate the attenuation, if you will, and therefore explain some of the clinical discrepancies. After all, most patients in the real world are on β blockers plus a nitrate. If there is a discrepancy between monotherapy and acute intervention studies and clinical responses, it may be that there's an interaction between the β blocker and the nitrates to modify the attenuation that's occurring.

Dr. Parker: I am not aware of any data that specifically assess the influence of β blockers on the development of nitroglycerin attenuation. Many of the patients that Reichek studied in *The American Journal of Cardiology* article in 1984 were on β blockers. Some of them actually were on calcium antagonists, too, I believe.

Dr. Scheidt: But the number of patients was very small. Eight patients in one group, 5 in another and 6 in a third.

Dr. Parker: And that was a short-term study, too. Patients were titrated up and then exercised over 24 hours. There was no long-term data.

Dr. Shell: Do you keep diaries on these patients? Is there a positive clinical response?

Dr. Parker: I tend not to place much reliance on diaries or counts of nitroglycerin consumption. First of all, patients don't keep diaries very well. They fill them out because the doctor wants them to, but they're rarely done reliably. Secondly, having been involved in this field of research for quite some time, I have found that patients tend to modify their life-style so as not to have anginal attacks. I've seen many patients who would develop angina between 3 and 8 minutes on the treadmill, but they were experiencing very little angina in their daily lives. They've learned to modify their life-style.

Dr. Shell: But these are very stable patients who probably have, in fact, no spontaneous anginal events.

Dr. Scheidt: Both treated and untreated, patients adopt a life-style that prevents angina. Indeed there might be better ways of doing a subjective assessment than diaries. If I were to do a subjective assessment, I wouldn't use a diary of the number of nitroglycerin tablets consumed or the number of anginal episodes. I'd use a pedometer, and find out how many steps patients walked or how many stairs they climbed. I think these are the parameters that patients would adjust in relation to their exercise capacity.

Dr. Shell: I'm not arguing, I'm just trying to get a feeling for the nature of the subset we're studying.

Dr. Parker: These are patients with stable, exercise-inducible angina who don't have pain at rest and who are off all medications except sublingual nitroglycerin used in the usual fashion.

Dr. Shell: And, therefore, one couldn't use normal clinical responses as indexes of how they would respond.

Dr. Scheidt: In other words, when you showed tolerance, for instance, in the isosorbide ointment group, were the patients still "better"—however that is defined—clinically?

Dr. Shell: Exactly. After all, one of the issues that's been raised is whether an objective method like Holter monitoring is relevant to patient care. This is a legitimate question. But then I would ask this question: Is exercise tolerance testing in a patient who is not experiencing anginal chest pain a relevant endpoint? Because these patients are not experiencing anginal chest pain, and therefore what does it matter that their exercise tolerance has gone from 3 minutes to 6 minutes?

Dr. Parker: As long as you know that they are truly not having angina. Perhaps these people are not having angina because they've lowered their levels of activity.

Dr. Scheidt: Dr. Parker made a comment that he didn't follow up. I want to raise it again now. You indicated that it might be the rate of rise of drug level that's important. Any comments on that?

Dr. Parker: Just a thought, I have no data.

Dr. Flaherty: It reminds me of the calcium-channel blocker story. If a patient has calcium blockers on board, and you give a large infusion of calcium, you can overcome the "block." You're not uncovering already covered receptors, but demonstrating competitive inhibition. Likewise, it may well be that during chronic nitrate therapy there may still be more nitrate receptors that do not have nitroglycerin bound to them. If you provide an additional drug, which could bind to these receptors, more vasodilator response might still be obtainable.

Dr. Weber: I have a question for Dr. Parker. You've undoubtedly looked at Thompson's paper[7] in some detail. The results are quite disparate from yours. I'm curious as to how your methodology differed from his, or how you would account for the difference in results and conclusions?

Dr. Parker: I haven't read that paper for a long time. John, you probably are more familiar with this.

Dr. Flaherty: One thing that has always struck me about it was that he selected for chronic study the responders from his acute study. In other words, he chose the nitroglycerin responders in the acute study to sublingual nitroglycerin. Thompson determined which patients were responding to nitroglycerin patches and then enrolled these people in the chronic study. This may harken back to a comment that I made previously. If one selects from a large population of patients with stable angina, there will be a group of people who will respond to low doses of nitrates. Thompson might have been lucky enough to find that subgroup. Parker, on the other hand, might have included by chance more patients requiring higher doses of nitroglycerin to obtain a significant antiischemic effect. Anytime you study a small number of patients and remembering the 20- to 40-fold variability in nitrate responsiveness from patient to patient, you can be lucky or unlucky in your selection of patients.

Dr. Weber: To use an infectious disease analogy, I think we're trying to determine whether a medication is an effective antibiotic for the treatment of pneumonia without knowing the causative organism. In angina, there seems to be a variety of types. We have many different medications, and just because an agent doesn't work for one patient, doesn't mean it may not be applicable and perfectly effective in yet another.

Dr. Selwyn: The best analogy by far is to hypertension. It has always been obvious that once a patient develops symptomatic hypertension, it is necessary to treat the symptoms and the background hypertension. It's taken years to work out that modest levels of essential hypertension, although asymptomatic, require treatment as well. This was shown in careful prognostic studies, insurance studies and population surveys. We have the same situation with angina. Remember, in essential hypertension, progress in treatment is being made without knowing the cause of the disease. So although

we do not know the precise cause of angina in each patient, we do know a group of mechanisms against which we can target drugs.

Need for Titration and Higher Doses

Dr. Selwyn: Now, if you want to try to arrive at the best dose for the nitrate patches, it would seem to me that, with what we know, you have to carefully titrate dose against ischemia in each patient and arrive, difficult though that may be, at an ideal dose for an individual.

Dr. Frishman: That's what we're involved with in our pilot nitroglycerin study. Each patient is titrated to his or her optimal patch dose.

Dr. Selwyn: But then you have to decide whether the dose-ischemia titration is relevant if it's done on an exercise test, because we don't run exercise tests all day out of the hospital. That is another issue.

Dr. Scheidt: There are, of course, other titrations that can be used. A number of the studies up to now have been done with what is called maximal tolerated dose, which is usually to intolerable headache.

Dr. Frishman: We are frequently dosing to 200 cm^2 (multiple patches) and patients are tolerating it very well. This is in contrast to Reichek who was claiming that patients were intolerant to the drug at 40 cm^2.

Dr. Parker: One of the problems is that Reichek was testing tolerable dose in an acute situation. After 10 days of therapy, you may be able to quadruple the dose, with good tolerance.

Dr. Flaherty: The other point is that most of Reichek's patients were receiving concomitant antianginal therapy. If you've already lowered blood pressure with calcium-channel blockers or β blockers, you've got very little left to drop. This would make it much harder to demonstrate a beneficial antiischemic effect of adding nitroglycerin.

I'd like to return to the subject of titration and stress that the reason why people are not titrating is that we have a very limited availability of patch sizes. The maximum patch size available now is 30 cm^2. Given the cost of a single patch, most physicians are unwilling to submit a patient to the cost of more than 1 patch a day. Therefore, there's an upper limit, a plateau if you will, to dosing. If there were a higher range of doses available, physicians might titrate higher. Given the inexpensiveness of nitroglycerin itself and the fact that what we are really paying for is the unit in which it's packaged, it would seem to me that any dose could be developed at approximately the same price. If we could establish in some research studies the range of doses that is clinically useful, then it would seem reasonable for the manufacturers to try to cover a large range of patch sizes. Then it wouldn't be so unreasonable to prescribe a dose of 20 to 50 mg/day (40 to 100 cm^2).

Dr. Scheidt: Titration is something that is commonly done with many other types of drugs, and for reasons I don't understand, probably because you get a month at a time in a box, titration is not something that's commonly practiced with patches. We have very good reason to believe that nitroglycerin doses are highly variable from patient to patient, and I now routinely titrate. I often will start with a 5-mg patch, and very quickly, certainly by the next month's prescription, will go up to a 10-mg patch. Frequently I even go higher than that. I think that for many patients—those in our studies, in the pilot studies of Dr. Frishman and in other reported studies—the maximal tolerated dose of nitroglycerin, even relatively short term, is probably above 15 mg. I think it's 15 to 25 mg, on average, in the population.

> ***"We have very good reason to believe that nitroglycerin doses are highly variable from patient to patient. . . . There will be very few patients who will get 'optimal' effect on a 5-mg patch, which I'm sure is the most commonly used dose."***
>
> ***—STEPHEN SCHEIDT***

Dr. Selwyn: It's much higher. My patients rarely use <60 mg.

Dr. Shell: But you're a tertiary referral center, and you see the worst patients.

Dr. Selwyn: The patients we see are referred by family practitioners.

Dr. Shell: But they're still on a referral basis. You're not seeing the patients who are doing well in the practitioner's office, who are not a problem to them.

Dr. Selwyn: But the potential is there to go up to 60 or 80 mg.

Dr. Scheidt: What we all do agree on is that there will be very few patients who will get "optimal" effect, whatever that is, on a 5-mg patch, which I'm sure is the most commonly used dose in the United States today. I think we all feel that we've been using the very lowest end of clinically relevant doses. Do we all feel that patches in doses of 50 mg would be useful?

Dr. Frishman: We think even higher than that, and a much wider dose range. In fact, from 5 to 100 mg.

Dr. Flaherty: A multicenter study is currently underway with such a dose range but results are several years off. We have some limited clinical data to suggest that higher doses will be useful but we can't be 100% sure. My own crossover data would suggest the development of a 50 or a 100 cm^2 patch.

Dr. Scheidt: To sound a note of caution, we know that we don't have the data in support of doses in excess of 100 cm^2. There's the possibility that larger and larger doses will simply chase one's tail and not be useful. I don't think we know for certain at the moment. I think what we do know is that many patients will tolerate higher doses.

Dr. Flaherty: There is a common misconception that going back to nitroglycerin ointment is the solution to the problem of nitroglycerin "tolerance." I find this very difficult to understand. It seems to me that ointment or oral preparations, given 4 or 5 times a day, should provide nitroglycerin blood levels very similar to those obtained with patches left on for 24 hours. How this would solve the problem of hemodynamic attenuation baffles me.

Dr. Weber: An even more peculiar anomaly is seen in our hospital. I see the house officers applying a transdermal patch and then adding to that isosorbide dinitrate every 6

hours. These patients are getting the worst of both possibilities; they're incurring the expense of the patch and at the same time the inconvenience of taking a medication 4 times a day.

> ***"Ointment, given 4 or 5 times a day, should be very similar to a patch left on for 24 hours. How this would solve the problem of hemodynamic attenuation baffles me."***
>
> ***—JOHN T. FLAHERTY***

Dr. Scheidt: I could see that the ointment might inadvertently provide a nitrate-free interval, because the ointment levels, especially at the end of 6 hours, are low. In addition, if patients sleep 8 hours and don't get up to put the ointment on, you might again be providing a couple of nitrate-free hours.

Dr. Flaherty: One other point is that during long-term therapy, compliance is not really 100%. Patients have probably been obtaining nitrate-free intervals for years by just forgetting to take 1 dose a day of oral or transcutaneous nitrates. No one has vigorously studied this, but I suspect that nitrate-free intervals have been there all the time.

Practical Clinical Applications

Dr. Roberts: Beta blockers have been mentioned a lot here. The disease, of course, is coronary artery disease, and it's my understanding that β blockers increase the total cholesterol level by 6 to 8%. The Lipid Research Clinic studies[8] have shown that when levels are diminished by 9%, the heart attack rate goes down about 19%. The difference between a 6 to 8% increase and a 9% decrease in lipid levels is an astronomical increase in heart attack rate. It would seem that a drug like nitroglycerin, which insofar as I know does not affect cholesterol levels, would be quite beneficial.

The question I have now is what recommendations do you have for the practicing cardiologist or clinician? I mean, the discussion of all the problems is nice, but if I had angina pectoris and came in to see you, would you prescribe these patches, for example, and if so, how would they be used? In terms of the tolerance issue, it seems to be that you can skip a day or so, or even hours, and then the patches seem to be fairly efficacious. What recommendations do you have for the practicing doctor?

Dr. Shell: It depends on whether you're seeing patients on a referral basis or for the first diagnosis of angina. Those are 2 separate circumstances. Let's start with the group of patients whom I see for the first diagnosis of angina. I try to get some assessment of their left ventricular function, by looking at their electrocardiogram, by physical exam and by chest x-ray. If I have reason to believe they have not had an acute myocardial infarction, which means they have an essentially normal ejection fraction, I start them on β blockade, then see them 2 weeks later. If they are still having chest pain, I add nitroglycerin, and I frequently use the patches because of compliance issues. I then see them 2 weeks later, and if they are pain free, I repeat their Holters, because I have access to that, and then I titrate their doses appropriately. Basically, I try to abolish angina. That's in the patients with normal ejection fraction. If I have reason to believe that they have a decreased ejection fraction, then I start them on nitrates first and titrate up to a maximally effective dose, which means anywhere from 10- to 25-mg patches. Then, if I have additional problems, I tend to use a small dose of a calcium-channel blocker if their ejection fraction isn't too low.

With patients who are referred to me and are already on antianginal medication, my approach depends on the problem. At that point the usual question is whether they are candidates for mechanical intervention, either percutaneous transluminal coronary angiography or surgery. Once I've determined this, I'm left with a cohort of patients who have not had surgical intervention. Then I go through the process of modifying their antianginal agents, which are a combination, in my judgment, of β blockade, nitrates and calcium-channel blockers. First I modify the doses using chest pain as the endpoint, and then I follow it up with ambulatory monitoring. And if I have 50 patients I will wind up with about 32 different regimens, because patients are very different.

Dr. Roberts: But with what you know about tolerance right now, are you going to keep the patches on continuously or are you going to, say, skip them on Saturday and on Sunday?

Dr. Shell: I tell them to get up in the morning, take their patch off, have breakfast and shower, and put their patch back on. That gives them about an hour to an hour and a half of a nitrate-free interval. Seeing Dr. Selwyn's data, I'm not sure that's the right time. Maybe I should be telling them to take it off at night. But practically speaking, taking the patch off for a short time in the morning seems to work very well. I don't know if that's right or wrong, because I haven't exercised them, but it seems like a reasonable approach. There are some patients who've evolved their own schemes and who will use 2 patches. They'll put one on in the morning, another one on at night, and take the second one off in the morning. They've learned to titrate their own dose, and they're a very interesting group of patients.

Dr. Selwyn: I think recommendations for the use of the patch are difficult at the moment, because the whole subject is just so nascent. I think one has to tell practitioners about the patch what you tell them for other drugs—that it's generally acceptable, it doesn't have troublesome side effects and they should continue to use it if it relieves the patient's pain. But I think with regard to timing, tolerance, pulsing etc., the whole subject is just too nascent to make any definitive recommendations.

Dr. Parker: I'd like to take a crack at the question Dr. Roberts posed. I'd take an entirely different approach from that which Dr. Shell outlined. Until someone shows me in a well-controlled study that silent ischemia can be corrected, and has anything to do with prognosis, I really don't care about that. I'm treating angina. I give patients isosorbide 3 times a day and nothing after the evening meal. We don't have patches in Canada but if we did, I would have them take the patch off when they get home from work and put it on after their morning shower, giving them a 12-hour nitrate-free interval. That's the way I would handle it. We talk a lot about silent ischemia, but no one has clearly shown that it is important in terms of prognosis, or that if you treat it, it modifies the prognosis. We're going to get into the coronary artery bypass problem pretty soon, because people will start treating it without really knowing.

Dr. Selwyn: But that's already happening. When young executives in responsible jobs present who have 4 mm of ST depression in a silent positive exercise test, they are already going to angiography and being bypassed for critical lesions. There are many cardiologists, some of the most famous in this country at Cedars-Sinai, who've said that it's such a high-risk situation it warrants immediate intervention. The other thing to keep in mind is that long before the exercise test was found to have prognostic value, it was being used to assess medical therapy. Its prognostic value has only recently been demonstrated. Even now there is no evidence that if drug therapy improves exercise test measures of ischemia, this will result in improved prognosis for the patient.

". . . what recommendations do you have for the practicing cardiologist or clinician? . . . how would you suggest the patches be used?"

—WILLIAM C. ROBERTS

Ambulatory 24-Hour Electrocardiogram Monitoring

Dr. Shell: Dr. Parker's position on the need to have the validity of silent ischemia demonstrated to him is quite appropriate from a scientific point of view, but I can assure him that once he starts getting Holters and sees patients with painless episodes of 4- or 5-mm ST-segment depression followed by runs of ventricular tachycardia, he's going to modify his position a bit. It's a very frightening finding and it can quickly change your perspective. So he's quite correct. Somebody does need to do a controlled trial that proves from a scientific point of view that Holter monitoring for silent ischemia has practical value. But Dr. Selwyn's position is also correct. This technology is not difficult. The practicing community will have access to ST-segment information from ambulatory electrocardiogram tapes relatively soon. It is not difficult to do, and, therefore, we're going to run into a problem very quickly where the practicing community is going to use it, probably with inadequate information.

Dr. Scheidt: Unfortunately, I have to respectfully disagree with you. It is not easy for the practicing physician to come by such data now, because a standard Holter, as we all know, is scanned for rhythm and rhythm only. The computer systems are not to be trusted in routine use. There are some Holter services that now give you an everybeat printout, but this is exceedingly difficult to use. So unfortunately, the data are very hard to come by, and I wish I knew what to recommend.

Dr. Shell: A point that needs to be made by everyone who is speaking on this issue is that the routine Holter, i.e., arrhythmia, monitoring, as given by these computer systems, should never be trusted for assessing ischemic electrocardiographic changes. That point needs to be made consistently.

Dr. Frishman: The other problem, and I've raised this with Dr. Selwyn, is that there is still tremendous variability, both intrapatient from day to day and interpatient, with this technique. And although we all have a classic patient with a reproducible type of phenomenon, that's really more often the exception, not the rule.

Dr. Scheidt: It took, after all, about 10 years for the day-to-day variability of ventricular premature complexes on arrhythmia Holter monitoring to be fully realized.

Dr. Shell: The data for beginning to assess Holters as a prognostic indicator probably already exist in all of our data pools. Most hospitals save their Holter tapes. Someone could go back, draw out those tapes and do a forward analysis of who did and did not survive.

Dr. Selwyn: The arrhythmia tapes in most hospitals are really not calibrated. The R wave is greatly amplified for analysis, so it distorts the ST segment and you get a lot of false-positives. There are, however, 1 or 2 studies in this country involving thousands of people with calibrated Holter tapes that have not been analyzed for ST-segment changes. So a study such as you recommend could be done.

Conclusions

Dr. Scheidt: It seems that the watchword of this symposium has been variability. Variability in patient selection, variability in pathophysiology of angina and variability in protocols. Let me refer briefly to how terrible the variability problem really is in terms of the findings. When you put it all together, it's not surprising that we should have no definite answer. The first thing that jumps out at you are the numbers—the numbers of patients in all the nitroglycerin patch studies are absurdly small. The mean is 10 to 12 patients. We talked about β error before. This is an enormously important point: the potential for difference between biological significance and statistical significance. And so, for instance, you see anomalies such as Reichek's, a study commonly perceived to be negative, which actually showed a 39% increase in exercise time. This used the maximal tolerated dose of transdermal nitroglycerin, a mean of 22 mg, and total exercise time as an index of efficacy. I've taken the FDA-approved measure of efficacy here—total exercise time—though we've all agreed there may be many other measures of efficacy that are more appropriate. We see a 39% increase in exercise time versus placebo, and yet because there are only 5 patients in the group, it's not statistically significant.

The second problem that's been alluded to several times is considerable variability in concomitant therapy. In Reichek's study, the patients were on other therapy. In several other studies they were not. There is no attempt among published reports to account for the possible impact of variations in concomitant medications on study results.

The third major problem in these studies is dose. In most cases, the doses used are rather small. This is true in both short- and long-term studies. If there is tolerance and such a low dose is then tested, I think it's not surprising to find a very small effect.

Some of the studies seem to be negative, and yet they show increases versus isosorbide. They show less in the way of ST-segment depression on 24-hour ambulatory electrocardiogram monitoring. With all the confusion that there seems to be then regarding variability in results, there are certainly a number of studies that show significant increases in exercise time early in treatment, and with somewhat more difficulty, show it later.

To sum up then, I think that objective efficacy in increasing exercise time is demonstrated frequently, and certainly in short-term studies. Efficacy is easy to show in the first 2 to 12 hours, and it's easy to show with larger doses. It's harder to show at 24 hours, but there are some positive trials, and interestingly, the positive trials have a reasonable number of patients. After long-term dosing, and really only long-term dosing has relevance to the clinical situation—the fact that you can show a change 4 hours after the first dose of nitro-

glycerin is interesting but unfortunately not very clinically useful—several studies show a significant increase in exercise time at both 2 to 4 and 24 to 48 hours. There are lots of scattered results that may or may not be positive depending on your bias. Again, I have put myself into the straightjacket that we have all been in up to now—using only the single parameter of exercise stress testing. And, of course, all of the studies had slightly different protocols and looked at slightly different parameters. Some did Holter monitoring and some did not.

In general, it's very difficult to draw definite conclusions. The clinical trials to date are small. Most, but not all, are randomized and blind; some, but not all, stopped other medications. Most of them used only 1 or 2 doses, and they were low doses. One of the things that's not an issue among the panel is that if you titrate transdermal nitroglycerin, every one of us is astounded at the doses we can reach. It's something I did not foresee when we started this research. Clearly there is not only great interpatient variability in the ability to receive nitroglycerin, but patients also have an enormous ability to receive nitroglycerin, so that the maximal tolerated dose has been surprisingly high. Regarding patient satisfaction and physician satisfaction, these are very soft data. We all agree on that and, I am afraid that as much as one would like to, it's difficult to find any significant way of interpreting this. We can, however, try to get a feel for what the soft data indicate. Most of the studies do keep angina counts, angina attack diaries and nitroglycerin counts, and many of them are favorable.

So there is more than a suggestion that patches are effective in certain groups of patients. I think the challenge of the next couple of years is, first, to find out if this is true in few, some or many patients. In addition, we will need to address such issues as proper dose, proper method of administration—nitrate-free interval or otherwise—and the proper endpoints to use. Should the method to assess efficacy be stress testing, should it be measurement of silent ischemia, should it be something else entirely? I think we have to conclude that we still have a great deal of work to do in this area to arrive at any definite conclusions, but hopefully we're on the way to resolving many of these problems.

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CME Test 1A

Symposium on Transdermal Nitroglycerin

Cornell University Medical College designates this continuing medical education activity for 5 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association. Answers are to be marked on the sheet on page 531.

1. What percentage of episodes of myocardial ischemia on 24-hour ambulatory electrocardiographic monitoring is asymptomatic?
   a) about 10%
   b) about 25%
   c) about 50%
   d) 66 to 75%

2. Episodes of silent ischemia on ambulatory electrocardiographic monitoring have median duration measured in:
   a) seconds
   b) minutes
   c) hours
   d) none of the above

3. A large proportion of episodes of silent ischemia on ambulatory electrocardiographic monitoring occur during:
   a) heavy physical exertion
   b) modest physical exertion
   c) anxiety
   d) none of the above

4. Episodes of silent ischemia seen during ambulatory electrocardiographic monitoring tend to be most prominent:
   a) during the first 4 to 6 waking hours of the day
   b) immediately after meals
   c) in the early evening
   d) during night time hours

5. Hemodynamic events occurring at or before the onset of episodes of silent electrocardiographic ischemia almost invariably include:
   a) increases in blood pressure
   b) increases in heart rate
   c) increases in both heart rate and blood pressure
   d) none of the above

6. Drug delivery with transdermal nitroglycerin patches depends on:
   a) location of the patch
   b) characteristics of the patient's skin
   c) skin blood flow
   d) none of the above

7. Possible reasons for inconsistent results regarding efficacy of transdermal nitroglycerin patches include:
   a) small number of patients studied per trial, averaging 10 to 15 patients per study
   b) use of maximal or submaximal stress testing rather than anginal attack rate or other ambulatory measure of efficacy
   c) possible attenuation or tolerance with continuous use of nitroglycerin
   d) all of the above

8. Hemodynamic effects of organic nitrates include:
   a) direct venodilation at low plasma concentrations
   b) direct arteriolar dilation at higher plasma and tissue concentrations
   c) coronary vasodilation
   d) all of the above

9. Nitrates:
   a) decrease endothelial cell production of prostacyclin
   b) interact with sulfhydryl groups on nitrate receptors on cell membranes
   c) are excreted by the kidney
   d) all of the above

10. Oral nitrates:
    a) must be given in large doses to overwhelm hepatic first-pass enzymatic breakdown
    b) often must be administered in doses higher than recommended by manufacturers
    c) have been associated with partial tolerance
    d) all of the above

11. Transcutaneous nitroglycerin, either ointment or patches, should be administered:
    a) through the skin of the anterior chest wall or proximal aspect of the upper limbs
    b) at the same skin site day after day
    c) at relatively low dose to avoid tolerance
    d) all of the above

12. Noncardiac effects of nitroglycerin include:
    a) increased gastrointestinal motility
    b) decreased esophageal spasm
    c) pulmonary bronchoconstriction
    d) none of the above

13. Adverse effects occasionally seen with nitroglycerin include:
    a) worsening angina from reflex tachycardia
    b) increased intracranial pressure
    c) mild nausea
    d) all of the above

14. Silent myocardial infarction:
    a) occurred in 15% of middle-aged men in Framingham
    b) made up 15% of transmural myocardial infarcts in Framingham
    c) occurs more often than myocardial infarction with symptoms in middle-aged American men
    d) none of the above

15. Episodes of transient asymptomatic ST depression on ambulatory monitoring:
    a) have been associated with perfusion defects on rubidium or thallium scanning when done during the episode
    b) are often related to electrolyte abnormalities
    c) have been shown to be artifactual and related to monitoring equipment in many cases
    d) all of the above

16. In various autopsy and angiographic studies, the incidence of significant coronary artery disease in asymptomatic and presumably healthy American men is about:
    a) 0 to 2%
    b) 2 to 5%
    c) 5 to 8%
    d) 8 to 10%

17. Diminution of some of nitroglycerin's effects when administered chronically is likely to be:
    a) attenuation, not true tolerance, because responsiveness to a "bolus" or acute increase in blood level (e.g., with an additional sublingual nitroglycerin) still persists
    b) less prominent for venodilating effects than other hemodynamic effects (i.e., reduction of preload persists even with prolonged and continuous usage)
    c) overcome by titrating and increasing the dose of nitroglycerin
    d) all of the above

18. Possible strategies to overcome potential nitroglycerin attenuation or tolerance include:
    a) increase in dosage when used chronically
    b) a nitrate-free interval
    c) reliance on transdermal nitroglycerin for less than 24 hours
    d) all of the above

19. N-acetylcysteine:
    a) has no hemodynamic effect of its own
    b) potentiates activation of guanylate cyclase by nitroglycerin, perhaps by making more reduced sulfhydryl groups available
    c) enhances nitroglycerin's vasodilator effects
    d) all of the above

20. A nitrate-free interval:
    a) has been shown effective in a few small studies in restoring exercise response to various nitroglycerin preparations including continuous long-acting isosorbide and transdermal nitroglycerin
    b) may require a substitute antiischemic agent during the interval, although definitive testing of this possibility is not available
    c) may allow release of nitroglycerin from oxidized receptors, and thus spontaneous reduction of the receptors, to restore nitroglycerin responsiveness
    d) all of the above

CME Test 1A: Answer Sheet

Symposium on Transdermal Nitroglycerin

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5.	a	b	c	d	15.	a	b	c	d
6.	a	b	c	d	16.	a	b	c	d
7.	a	b	c	d	17.	a	b	c	d
8.	a	b	c	d	18.	a	b	c	d
9.	a	b	c	d	19.	a	b	c	d
10.	a	b	c	d	20.	a	b	c	d

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A Symposium: Laboratory Lipid Values

Editor:
Scott M. Grundy, MD, PhD

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A Symposium: Laboratory Lipid Values

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A Symposium: Laboratory Lipid Values

Introduction

SCOTT M. GRUNDY, MD, PhD

In recent years there has been increasing interest in the role of plasma cholesterol and lipoproteins in the causation of coronary artery disease (CAD). The relation between a high level of plasma cholesterol and rates of CAD is now well established. There is also growing evidence that specific lipoproteins are involved in the atherogenic process. For instance, the low density lipoproteins (LDLs) have been identified as the most highly atherogenic of the lipoproteins. The high density lipoproteins actually may be antiatherogenic, as high levels of high density lipoproteins appear to be protective against CAD.

The relation between the plasma lipoproteins and CAD has been established mainly through epidemiologic studies. On the basis of these studies, general recommendations have been made about changes in diet and life-style that will modify the metabolism of lipoproteins and thus may protect against atherosclerosis. However, many investigators have been uncomfortable with recommendations made without proof that actual modification of lipoprotein levels will alter the risk for CAD. In recent years, several clinical trials have provided supporting evidence that "favorable" alterations in lipoprotein levels actually decrease the risk for CAD. Of particular importance was the recent Lipid Research Clinics Coronary Primary Prevention Trial. This trial demonstrated that lowering of LDL levels does decrease rates of CAD. This finding has greatly stimulated interest in prevention of CAD through alteration of cholesterol (and LDL) levels.

In the wake of this trial, the National Institutes of Health convened a Consensus Conference on Cholesterol, which resulted in the issuance of a report indicating that elevated cholesterol levels are a significant risk factor for CAD. Further, it was recommended that both physicians and the general public take steps to reduce cholesterol levels, focusing in particular on patients with elevated levels.

In light of this, several distinguished physicians, laboratory directors and biochemists were invited to address critical issues in the evaluation of patients suspected of having lipid disorders and in the interpretation of laboratory values for these individuals. Specific questions addressed by the panel included: what are lipoproteins and how should they be tested; what is the reliability of lipoprotein testing; what should be considered a normal range for plasma lipids and lipoproteins; and, finally, who should be tested and how should results be interpreted?

It is the intent of this symposium supplement to provide a discussion of the problems confronting the clinical laboratory in the accurate measuring of lipids and lipoproteins, and in the reporting of these values in a useful way to the physician.

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Classification and Structure of Lipoproteins

ANTONIO M. GOTTO, Jr., MD, PhD

The lipoproteins were first discovered in the late 1920s by Macheboeuf who used ammonium sulfate precipitation to separate and fractionate the lipoproteins.[1] In the 1940s, they were further studied, first by Oncley and his group at Harvard, using Cohn fractionation, and later by Gofman and associates at the Donner Laboratory in California. Gofman et al[2] used analytical ultracentrifugation to separate the lipoproteins based on their rate of flotation in the ultracentrifuge. In the mid-1950s, Havel, Eder and Bragdon[3] introduced preparative ultracentrifugation, which remains the classic way of separating the plasma lipoproteins. In the 1960s, Hatch and Lees used albumin in buffer, which resulted in a much cleaner separation of the lipoproteins on paper electrophoresis. This technique was subsequently adopted by Fredrickson, Levy and Lees,[4] who used electrophoresis along with preparative ultracentrifugation and heparin manganese precipitation as the basis of a system for phenotyping the plasma lipoproteins.

The introduction of a simple system for classifying plasma lipoprotein disorders based on phenotypes helped to generate an outburst of interest in research in the plasma lipoprotein field (Table I). More recently, zonal centrifugation for dividing lipoprotein classes into subgroups and the use of monoclonal antibodies to identify apolipoproteins have been introduced.

The plasma lipoproteins are macromolecular complexes held together by noncovalent, primarily hydrophobic, forces, and serve as the carriers of lipid in plasma. With the exception of the fatty acids, which are carried by albumin, all of the plasma lipids are transported in association with plasma lipoproteins.

One of the functions of this group of particles is to serve as a detergent to solubilize and protect the water-insoluble lipids—cholesteryl esters and triglycerides—as they are carried in the blood. The major lipid components of the plasma lipoproteins are phospholipids, cholesterol, cholesteryl esters and triglycerides. Table II lists the composition of each lipoprotein class. The protein components are called apolipoproteins.

Lipoproteins appear as spherical particles, with the water-insoluble lipids at the center or core, when observed with the electron microscope. They are surrounded by a surface monolayer consisting of the apolipoproteins and the polar parts of the phospholipids. It is believed that cholesterol lies somewhere between the surface monolayer and the central core of the neutral lipid (Fig. 1). The apolipoproteins seem to contain specific lipid-binding regions called amphipathic helixes; apparently, these are the sites that serve for interaction in binding between the apolipoprotein and the phospholipid.

Five major classes of the plasma lipoproteins have been identified (Table II). The basis for their classification and separation remains the ultracentrifuge and electrophoresis. Chylomicrons are the largest of the particles, and are made in the gut. They reach the circulation by the lymphatic system and carry the dietary triglyceride and cholesterol.

The next largest particles are the very low density lipoproteins (VLDLs), which are made in the liver. They carry triglyceride and cholesterol, are synthesized within the body and serve as a major transport system for the endogenously synthesized triglycerides. On electrophoresis, VLDLs lead the beta globulins in migration; thus, they are also called the pre-β lipoproteins.

Smaller than VLDLs, the intermediate density lipoproteins are the family between VLDLs and low density lipoproteins (LDLs). It is thought that they represent intermediate stages in the conversion of VLDLs to LDLs.

The fourth group, and one of the most significant with regard to arteriosclerosis, is the LDLs. LDLs are the major cholesterol carriers in the blood, and are synthesized primarily in the liver. Their major protein constituent is apolipoprotein B. The LDLs migrate with the β globulins and are also called β lipoproteins.

The fifth family of lipoproteins is the high density lipoproteins (HDLs). They are also called α lipopro-

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TABLE I Hyperlipoproteinemia Phenotype Definitions and Their Association with Genetic and Other Disorders

Phenotype	Common Name	Laboratory Definition	Associated Genetic Disorders	Conditions Associated with Secondary Hyperlipoproteinemia
Type I	Exogenous hyperlipidemia	Hyperchylomicronemia and absolute deficiency of lipoprotein lipase or postheparin lipolytic activity Cholesterol normal Triglycerides greatly increased	Familial LPL deficiency ApoC-II deficiency	Dysglobulinemia, pancreatitis, poorly controlled diabetes mellitus
Type IIa	Hypercholesterolemia	LDLs increased Cholesterol increased Triglycerides normal	Familial hypercholesterolemia LDL receptor abnormal Familial combined hyperlipidemia Polygenic hypercholesterolemia	Hypothyroidism, acute intermittent porphyria, nephrosis, idiopathic hypercalcemia, dysglobulinemia, anorexia nervosa
Type IIb	Combined hyperlipidemia	LDLs increased VLDLs increased Cholesterol increased Triglycerides increased	Familial hypercholesterolemia Familial combined hyperlipidemia	
Type III	Dysbeta-lipoproteinemia	Floating β-lipoproteins VLDL cholesterol/VLDL triglyceride >0.35 ApoE-II homozygote on isoelectric focusing Cholesterol increased Triglycerides increased	Familial dysbeta-lipoproteinemia	Diabetes mellitus, hypothyroidism, dysglobulinemia (monoclonal gammopathy)
Type IV	Endogenous hyperlipidemia	VLDLs increased Cholesterol normal or increased Triglycerides increased	Familial hypertriglyceridemia Familial combined hyperlipidemia	Glycogen storage disease, hypothyroidism, disseminated lupus erythematosus, diabetes mellitus, nephrotic syndrome, renal failure, ethanol abuse
Type V	Mixed hyperlipidemia	Chylomicrons and VLDLs increased LDLs present but reduced Cholesterol increased Triglycerides greatly increased	Familial hypertriglyceridemia Familial multiple lipoprotein-type hyperlipidemia	Poorly controlled diabetes mellitus, glycogen storage disease, hypothyroidism, nephrotic syndrome, dysglobulinemia, pregnancy, estrogen administration (either contraceptive or therapeutic) in women with familial hypertriglyceridemia

LDL = low density lipoprotein; VLDL = very low density lipoprotein.
From Gotto AM. Practical approach to phenotyping hyperlipoproteinemia. In: Kligfield PD, ed. Cardiology Reference Book. New York: CoMedica, 1984: 46–47.

TABLE II Chemical Composition of Normal Human Plasma Lipoproteins

	Surface Components (mol%)			Core Lipids (mol%)	
	Cholesterol*	Phospholipids	Apoproteins	Triglycerides	Cholesteryl esters
Chylomicrons	35	63	2	95	5
VLDL	43	55	2	76	24
IDL	38	60	2	78	22
LDL	42	58	0.2	19	81
HDL_2	22	75	2	18	82
HDL_3	23	72	5	16	84

* May be distributed between the surface and core and, in the case of large chylomicrons, more cholesterol may be in the core than on the surface.
HDL = high density lipoprotein; IDL = intermediate density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein.
From Smith LC, Massey JB, Sparrow JT, Gotto AM Jr, Pownall HJ. Structure and dynamics of human plasma lipoproteins. In: Pifat G, Herak JN, eds. Supramolecular Structure and Function. New York: Plenum, 1983: 213.

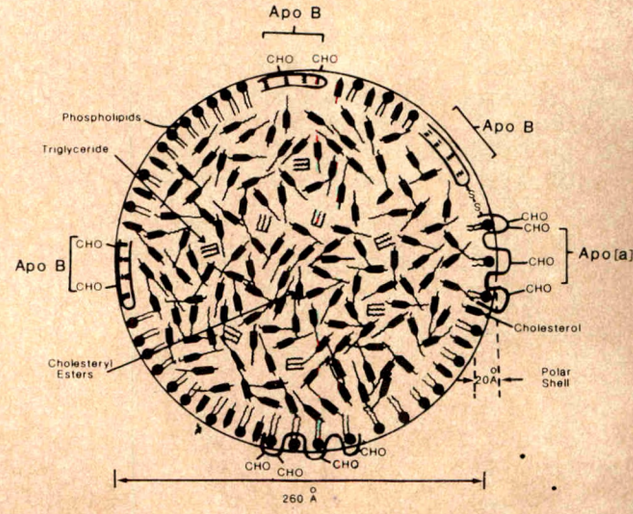

FIGURE 1. Model of lipoprotein [a] molecule illustrating the spatial relation of the neutral lipid core to the polar lipid shell. Courtesy Baylor College of Medicine.

teins because they migrate with the α globulins. The HDL family members are relatively rich in protein; they contain approximately one-half protein and one-half lipid, by weight. The major lipid constituents are phosphatidylcholine or lecithin and cholesteryl ester. They are subdivided into 2 categories, HDL_2 and HDL_3. This subdivision may be important in relating the relative protection of HDLs to coronary artery disease.

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Relation of Elevated Blood Lipid Levels to Development of Atherosclerotic Plaques

WILLIAM C. ROBERTS, MD

At least 6 factors indicate that elevation of the blood cholesterol level (particularly the low density lipoprotein [LDL] component that is reflected by the plasma or serum total cholesterol) is essential for the development of arterial atherosclerotic plaques large enough to cause organ ischemia:

1. Atherosclerotic plaques in both human and nonhuman animals contain cholesterol esters;
2. Atherosclerotic plaques can be produced in certain nonhuman animals (e.g., baboons, monkeys, rabbits) by feeding these animals diets high in cholesterol and saturated fats;
3. In nonhuman animals that have developed atherosclerotic plaques as a result of being fed diets high in cholesterol and saturated fats, the atherosclerotic plaques regress when the atherogenic diet is discontinued;
4. Persons who have extremely elevated total serum cholesterol levels (>500 mg/dl), in which the dominant component is LDL cholesterol, have extensive atherosclerosis at an early age. (These persons have homozygous type II hyperlipoproteinemia.) Without effective lipid-lowering therapy, these persons usually die from consequences of severe atherosclerosis before the age of 20. In other words, when the LDL is greatly elevated, the amount of atherosclerotic plaque is extensive and develops at an early age. The greater the quantity of LDL cholesterol in the blood, the greater the quantity of atherosclerotic plaque on the arterial wall.
5. Individuals with low (<150 mg/dl) total serum cholesterol levels have no or insignificant amounts of atherosclerotic plaques. Necropsy studies of the coronary arteries, aorta and circles of Willis in populations with total serum cholesterol levels <150 mg/dl (from certain parts of Asia and Africa) have demonstrated few or no atherosclerotic plaques.
6. Lowering the blood cholesterol level, when it has been significantly elevated, has been demonstrated to lower the frequency of development of symptomatic or fatal coronary events. The Lipid Research Clinics Coronary Primary Prevention Trial has unequivocally demonstrated that when the plasma total cholesterol is lowered in persons with high levels (>265 mg/dl), the frequency of fatal and nonfatal myocardial infarction, sudden coronary death, angina pectoris, positive exercise stress test and need for coronary artery bypass surgery is reduced.[1]

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Reference

1. Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251:365–374.

Discussion

Dr. Grundy (Dallas, Texas): Dr. Gotto, could you summarize the major points that clinicians should be aware of concerning lipoproteins?

Dr. Gotto (Houston, Texas): The physician needs to know which lipoprotein families are associated with coronary disease and which are relatively protective against it. Dr. Roberts mentioned the strong evidence associating high levels of low density lipoprotein with the prevalence and severity of coronary artery disease. There is an inverse relation that is now well known and well characterized between high density lipoproteins and coronary disease.

Beyond that, I think that the physician needs to know that chylomicrons are the particles that carry the dietary triglyceride and that they may be elevated in some individuals after a fatty meal. The triglycerides that are made in the body are carried in the very low density lipoproteins. So if one eliminates chylomicrons, a measurement of triglyceride is primarily associated with the level of the very low density lipoproteins.

Dr. Grundy: Dr. Cooper, did you have a comment?

Dr. Cooper (Atlanta, Georgia): Yes. Both Drs. Gotto and Roberts mentioned the risk associated with most of the lipoproteins, but the risk associated with very low density lipoproteins, cholesterol and cholesterol remnants was not mentioned. I wonder if very low density lipoprotein and triglycerides are associated with coronary artery disease risk, through the low density lipoprotein cholesterol as well as through the increased metabolic reactions?

Dr. Gotto: Yes, I think that while triglyceride as an independent risk factor has not been definitively proven in epidemiologic studies, elevations of triglyceride are associated with other factors and metabolic problems that we know are themselves associated with an increased risk of coronary disease. There is also a statistically reciprocal relation between triglycerides and high density lipoprotein. The higher the triglyceride factor, the relatively lower the concentration of high density lipoprotein. It is possible to factor out triglycerides in a multifactorial analysis, but it does not necessarily mean a high level is safe. But the risk of triglycerides is probably related to other metabolic problems, which themselves predispose a person to increased risk of coronary disease progression.

Dr. LaRosa (Washington, D.C.): We have to consider when intervention is necessary in patients whose cholesterol levels are elevated. We have known for some time that there are early lesions in adolescents and in young adults that do not have the same complexity as arteriosclerotic lesions in older people do. Can you tell us whether those lesions do, in fact, progress? Does the presence of lesions provide us with any guidance about whether or not we should be considering intervention in young adults?

Dr. Roberts (Bethesda, Maryland): We have found lipid lesions in teenagers and adults in central Africa. These teenagers had very low cholesterol levels, generally about 100 or 110 mg/dl. In the United States, the occurrence of lipid lesions in teenagers is relatively common. These lipid lesions do not progress to fibrous or complicated plaques in the population groups where the total cholesterol levels are 110 or 120 or certainly under 150 mg/dl. In most people in this country, fibrous lesions begin developing in coronary arteries during adolescence, whereas they do not in those populations where the lipid levels are low. I am not convinced, however, that these minor lipid lesions are really precursors of the plaques that become large enough to narrow arteries.

It is important to realize that atherosclerosis is an intimal lesion and that these early plaques contain a great deal of lipid. On the other hand, in the person aged 70 who has a fatal acute myocardial infarction or sudden coronary death, the dominant component of the arteriosclerotic plaque is not lipid, but collagen.

Dr. Grundy: Dr. Gotto, you have already identified low density lipoprotein as the major atherogenic lipoprotein. We know of the exciting finding that most of the low density lipoprotein is removed from the circulation by receptors on the surface of cells. What role do you think these receptors play in the development of arteriosclerosis or in the overall causation of high cholesterol levels?

Dr. Gotto: I think that the low density lipoprotein receptor or the specific low density lipoprotein receptor as it was first discovered by Brown and Goldstein[1] plays primarily a protective role by lowering the level of low density lipoprotein and low density lipoprotein cholesterol circulating in the blood. There is a nonspecific pathway, in which cholesterol and low density lipoprotein are removed, but probably one-half to two-thirds of the low density lipoprotein and low density lipoprotein cholesterol are removed via the specific pathway. This receptor may be affected by diet, drugs and various factors that alter the intracellular level of cholesterol.

For example, one lipid-lowering agent pulls out the bile acids from the intestine into the stool. By lowering the level of bile acids, the level of cholesterol decreases within the cell, within the liver. The cell responds to this decrease in intracellular cholesterol, we believe, by making more receptors, and as it makes more receptors, the liver is able to pull more low density lipoprotein out of the blood. So, the type of diets or types of medications that decrease the level of cholesterol within the liver would be expected to increase in the activity of the low density lipoprotein receptor, and decrease the concentration of low density lipoprotein. Then, based on the cholesterol or lipid hypothesis, as stated by Dr. Roberts, this would decrease the risk of cholesterol and low density lipoprotein deposition in arteries.

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Reliability of Lipid and Lipoprotein Testing (I)

HERBERT K. NAITO, PhD

The accuracy and precision (within-day and day-to-day reproducibility) of lipid and lipoprotein tests must be considered in addressing the question of reliability. Most analytical variance is classified as either systematic or random. Systematic variance includes variations that influence observations consistently in one direction or another. Systematic variance may arise from either natural or man-made events of which the investigator may or may not be aware. The sources of systematic variance are aging, personal bias of the analyst, laboratory bias, inter- and intraindividual bias and experimental error.

Random variance includes variations whose sources cannot be completely identified and controlled and are considered to be due to chance. The fluctuations may be in either direction (i.e., positive or negative bias). The chance for random error may be affected by the quality and source of reagents, the number and complexity of the steps in a procedure and the skill of the analyst performing the test. An example of this would be analyses of the same specimen, made in exactly the same way by the same analyst, yielding different results.

A system is said to be in a state of statistical control when systematic variance, random variance and the interaction between the sources of variance have been evaluated and judged to be within acceptable limits. This does not eliminate all the variability in the data, but the remaining variance is considered unimportant and reasons for its occurrence are not sought.

The reliability of lipid and lipoprotein testing can be addressed by examining survey data. Most laboratories are enrolled in proficiency testing. Two major organizations testing laboratory proficiency are the College of American Pathologists and the Centers for Disease Control (CDC). The precision or reproducibility of an assay can be readily assessed by the laboratory performing the test. Most total cholesterol assays today have within-day precision of <4% (coefficient of variation [CV]) while day-to-day precision is slightly higher, e.g., about 3 to 6% CV. With a great amount of care, one can achieve a within-day precision of ≤2% and a day-to-day precision of ≤3%.[1]

The CDC has proposed a modification of the procedure of Abell et al[2] for use as a reference method for cholesterol. This method includes hydrolysis of the cholesteryl esters, extraction with petroleum ether and color development with acetic acid-acetic anhydride-sulfuric acid reagent. With proper equipment and good technical skills, this procedure can be used to produce accurate, precise results. The alterations recently instituted allow for simultaneous analysis of a greater number of samples than was previously possible, using improved instrumentation. The CDC still utilizes this method for the assignment of "target values" on serum-calibrating materials and on quality control materials.

One way to examine how accurately laboratories perform lipid analyses is to look at proficiency surveys. The 1974 findings of the CDC proficiency testing program indicated that a large variation in results was obtained when assayed serum samples were sent to 263 licensed clinical laboratories, 250 volunteer clinical laboratories and 80 reference laboratories for total cholesterol and triglyceride determinations. Values varied by as much as ±20 to 30 mg/dl for cholesterol and ±25 to 40 mg/dl for triglycerides. This suggests that accuracy still poses a problem.

Data from the College of American Pathologists suggest that the precision of total cholesterol and triglyceride methods has improved over the years, but accuracy and interlaboratory comparability are still problematic. A recent College survey suggests that interlaboratory comparability can be further improved. For example, the mean range in values for a single cholesterol specimen was 298 ± 28.5 to 376 ± 17.1 mg/dl (mean ± standard deviation). Triglyceride values ranged from 260.4 ± 43.8 to 362.5 ± 51.2 mg/dl for 1 specimen, and from 197.6 ± 30.5 to 282.1 ± 32.7 mg/dl for another. The high density lipoprotein cholesterol results (Table I) are also a problem; the range of 25.5 ± 2.7 to 30.7 ± 4.8 mg/dl represents about a 20% difference.

These large deviations in values clearly indicate the need to improve the accuracy, precision and interlaboratory comparability of lipid and lipoprotein assays. With more than 95% of clinical laboratories perform-

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ing cholesterol determinations by enzymatic means, a multitude of instrumentation/enzymatic reagent combinations are contributing to the variability of values. Previous surveys have demonstrated that the methodology, reagent source, instrumentation, standardization technique, type of standard or calibrator used can affect the accuracy and precision of interlaboratory cholesterol measurements.[3,4]

Standardization of Lipid Research Clinics' Data

Interlaboratory performance can be significantly improved when a common standardization material is used. This was clearly proved when the CDC assisted in standardizing the 12 Lipid Research Clinics (LRC) to help minimize interlaboratory and intralaboratory variability.[5] The 12 LRC laboratories used identical methods, standards, calibrators, internal quality control procedures and blind external surveillance methods. The results were compared with the reference cholesterol method.[2] The LRC laboratories also used the same sequence of standards and common procedures for instrument start-up, instrument calibration and analysis. The average cholesterol bias for the 12 laboratories was −1.3% and ranged from −0.5 to −2.0% when compared with the reference values of Abell et al.[2] The overall results indicated that a high degree of accuracy, precision and interlaboratory comparability was achieved through the rigorous standardization and control of the entire analytical procedure in the LRC laboratories. In addition, the average bias was very small and probably approaches the practical limits of accuracy that can be achieved in any collaborative multilaboratory study.

The results show that collaborative studies involving laboratories throughout the country can be done in such a way that resulting data can be legitimately pooled for analysis. Care must be taken in standardizing methodology, evaluation criteria, control pools, calibration material, etc. Internal and external quality control programs should also be implemented to monitor and assess the performance and comparability of various laboratories.

Reliability of High Density Lipoprotein Cholesterol Measurement

The CDC published a survey report that examined 130 laboratories in relation to their methods and performance in measuring high density lipoprotein cholesterol.[6] Of the 130 participating laboratories, 79 were classified as medical service, 12 as commercial analytical service, 8 as manufacturer research and development, 18 as lipid research and 12 as LRC laboratories; one was the CDC Lipid Reference Laboratory. Thus, about 60% of the reported results were generated from clinical laboratories performing diagnostic services in medical clinics or hospitals. The findings suggest that high density lipoprotein cholesterol testing is not satisfactory in many laboratories. Although most survey laboratories demonstrated adequate precision, 53% of the mean results deviated from the mean (34.5 mg/dl) of the low level high density lipoprotein cholesterol pool by >7.5% (CV). Thus, accuracy was inadequate for most laboratories. Over the entire range of high density lipoprotein cholesterol concentrations (34.5 to 59.6 mg/dl) used in the survey, 62% of the laboratories had a mean difference for one or more pools that exceeded 7.5% of the overall mean, while 50% of the laboratories exceeded 10% of the overall mean on one or more pools. Wide laboratory variation in results within some facilities suggests that poor analytical technique was responsible. The data also implied that some laboratories did not, or could not, calibrate properly.

TABLE I College of American Pathologists Comprehensive Survey (1984 participant summary)

Constituent Method/System	Labs (n)	Mean	SD	CV (%)
	Specimen C-24			
HDL cholesterol (mg/dl)				
Herparin/Mn/Ca W/Enz Quant	113	30.7	4.8	15.5
Phos/mg with Enz Quant	998	27.4	4.2	15.2
Phos/mg Non-Enz Quant	29	28.1	5.8	20.6
Dextran sulfate (500,000#MW)/mg	188	25.5	2.7	10.7
Dextran sulfate (50,000#MW)/mg	32	26.9	3.0	11.0
Dextran sulfate (other MW)/mg	149	26.7	4.0	15.0
Electrophoresis-densitometer	99	32.7	7.4	22.6
All method principles	1,642	27.6	4.5	16.3

CV = coefficient of variation; HDL = high density lipoprotein; SD = standard deviation.

Clear-cut differences owing to the methodologies used were not defined, with the exception of the electrophoresis procedures, which were imprecise and differed widely among laboratories. The CDC concluded that considerable improvement in high density lipoprotein cholesterol measurement is needed by many laboratories.

One of the major problems in many laboratories is the lack of appropriate reference material to use in determining the accuracy of their methods. In this respect, the CDC has been an invaluable resource as a lipid reference laboratory. The major thrust in their cholesterol and triglyceride standardization program, begun over 2 decades ago, was to ensure that the lipid and lipoprotein chemistries of the laboratories participating in the LRC program were rigorously standardized in terms of accuracy and precision. Since then, the CDC has allowed other, non-LRC centers to participate in its standardization and certification program and has offered its assistance in solving analytical errors to many nonparticipating members. Assayed, pooled control sera with "target values" established by reference procedures (and recently cross-checked by definitive methodology) are available for those who wish to determine the accuracy of the lipid tests used in a laboratory. Acknowledging the data of the 1980 CDC report[6] on high density lipoprotein cholesterol measurements, the CDC has begun a standardization and certification program to include high density lipoprotein cholesterol measurements to help reduce the errors associated with this test. This undertaking is important because many clinical laboratories use normal ranges or coronary artery disease risk tables based on the LRC studies.

The low density lipoprotein cholesterol/high density lipoprotein cholesterol ratio for coronary artery dis-

ease risk was developed from the Framingham data base.[7,8] The methods used in the Framingham studies were rigorously standardized by the CDC. The mean difference in plasma high density lipoprotein cholesterol concentration between those subjects confronted with coronary artery disease and those apparently normal was about 4.3 mg/dl.[8] This small difference between the 2 populations highlights the importance of ensuring that the high density lipoprotein cholesterol method is highly precise so that analytical tests reveal the true sensitivity and specificity of the method. In addition, because the high density lipoprotein cholesterol determination, high density lipoprotein cholesterol/total cholesterol ratio and low density lipoprotein cholesterol/high density lipoprotein cholesterol ratio risk tables now being used by physicians are based on the Framingham study, it is essential that clinical laboratories execute high density lipoprotein cholesterol determinations with the same accuracy and precision.

High density lipoprotein cholesterol is generally measured as the cholesterol in the supernatant solution after precipitation of apo β-containing lipoproteins. According to the College of American Pathologists (Table I), the sodium phosphotungstate method is most commonly used in the clinical laboratory. Dextran sulfate with magnesium is another precipitation procedure in use. This method was recently reported as a selected method for high density lipoprotein cholesterol testing; it was designed to optimize the conditions for removing low density lipoprotein and very low density lipoprotein, the apo β-associated lipoproteins, without excessive high density lipoprotein precipitation.[9] The dextran sulfate and heparin-$MnCl_2$ methods are generally considered the comparison methods because previous studies demonstrated good specificity for high density lipoprotein separation.[9,10]

Although electrophoresis gives a positive bias (Table I), it is still used as a means of high density lipoprotein cholesterol quantitation.[11] While conceptually it has the advantage of simultaneously obtaining the cholesterol concentration in the electrophoretically separated lipoproteins, electrophoresis is inaccurate and imprecise. This methodology should be discouraged because of the availability of other more reliable methods.

Recently, Warnick et al[12] evaluated "second generation" high density lipoprotein methods to assess their agreement on normolipidemic specimens, and on specimens with high and low concentrations of cholesterol, triglyceride and high density lipoprotein. The methods were compared using specimens with a wide range of total cholesterol, triglyceride and high density lipoprotein cholesterol values. Their study suggested that dextran sulfate, heparin-$MnCl_2$ (92 mmol/liter) and phosphotungstate-$MgCl_2$ procedures yield similar results.

It should be emphasized that high density lipoprotein cholesterol quantitation has 2 stages: isolation of the high density lipoprotein and measurement of the cholesterol in the isolated high density lipoprotein. While the first phase can be accomplished relatively easily with care and appropriate precipitating agents, the second phase can cause analytical problems; i.e., the salts used can cause interference with the cholesterol measurements, depending on the specific method selected.

Reliability of Triglyceride and Low Density Lipoprotein Measurement

The assay of triglycerides poses more problems in the general clinical laboratory. Few laboratories in the United States correct for free glycerol concentration. This has important implications in determining low density lipoprotein cholesterol because it is estimated from very low density lipoprotein cholesterol. Most clinical laboratories, for convenience, indirectly estimate very low density lipoprotein and low density lipoprotein cholesterol using the Friedewald formula, which hinges on the assumption that very low density lipoprotein cholesterol approximates *plasma* true triglyceride divided by 5. From this calculation LDL-C can be calculated as LDL-C = total C − (VLDL-C + HDL-C), where LDL is low density lipoprotein; C is cholesterol; VLDL is very low density lipoprotein; HDL is high density lipoprotein.

There are several technical problems with this technique. First, the Friedewald formula does not apply to all persons. Second, the formula is based on true triglyceride determination. Most laboratories measure total glycerol and report the value as "triglycerides." These laboratories do not want to measure true triglycerides because of the cost, inconvenience, time and the false assumption that the free glycerol level in the blood is small and relatively constant. While most nonstressed healthy persons may have free serum glycerol concentrations of 8 to 20 mg/dl, it is not uncommon to find values >75 mg/dl.[1] Thus, it is easy to see that when inaccurate triglyceride values are obtained, the estimated very low density lipoprotein cholesterol value is incorrect, leading to inaccurate estimates of low density lipoprotein cholesterol. It should also be remembered that the Friedewald formula does not apply when true triglyceride values are >400 mg/dl.

For an accurate triglyceride level, the free glycerol of the sample should be subtracted from the total glycerol (both free and that produced from saponification of the triglycerides) by a blanking procedure. Inspection of the current proficiency survey of the College of American Pathologists indicates that less than 1% of the participants correct for free glycerol in the blood. Quantitative analysis for triglycerides in serum and plasma is commonly done by hydrolyzing the triglycerides and then determining glycerol enzymatically or chemically. When this is done, however, not only glycerol derived from the triglycerides but also the unesterified "free" glycerol is measured. Either 2 analyses must be performed, one before and one after the hydrolysis step, or the 2 serum constituents have to be separated by extraction or by solvent partition.

Glycerol primarily comes from the adipose tissue via lipolysis of stored triglycerides. The triglyceride lipase that regulates the rate of triglyceride breakdown to free fatty acid and glycerol is sensitive to hormones. Epinephrine, glucagon, thyroxine and growth hor-

mone will potentiate the activity of this enzyme, which, in turn, causes more free fatty acid and glycerol output into the blood. It is understandable, then, that any stressful situation creates a situation in which a high free glycerol concentration can occur. Some known conditions that can contribute to high glycerol levels in the blood are stress (epinephrine effect), mannitol infusion, treatment with nitroglycerin, diabetes mellitus, glycerol-coated stopper used in Vacutainer tubes®, certain liver diseases and hemodialysis in cases of renal failure.[1] Because there is a risk involved in calculating the free triglyceride concentrations by using factors of percentages, glycerol blanking is necessary for accurate triglyceride analysis.

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Reliability of Lipid and Lipoprotein Testing (II)

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There is enormous interest in the measurement of blood lipids, both by physicians and by patients. Proficiency testing of laboratories by the College of American Pathologists and the Centers for Disease Control (CDC) has provided a large data base concerning such measurements. Examination of these data reveals that laboratories perform in an acceptable way. However, in the College's surveys, the coefficient of variation (CV) for cholesterol measurements averages about 6%. A 6% CV means that there is a 95% probability that a cholesterol value of 260 mg/dl will be reported between 229 and 291 mg/dl. The survey shows further that the CV itself may vary from 2.5 to 9.5%, depending on the laboratory, method and instruments. A cholesterol value of 260 mg/dl with a CV of 9.5% will be reported in a range of 210 to 309 mg/dl.

Similar data can be obtained from the CDC's proficiency testing, where the CV has been reported to average from 9 to 10%. At a cholesterol level of 135 mg/dl, a 10% CV implies reported values ranging from 108 to 162 mg/dl. The CDC data also show that the CV ranged from 3 to 18% in different laboratories.

The data are distressing, but physicians and patients see less variability in results since, generally, a patient's cholesterol is analyzed in a single laboratory, and the precision data from a single laboratory are much better than the proficiency data derived from all laboratories. For example, our laboratory performs 10,000 cholesterol assays a day. Our internal quality control measures indicate that at a level of 150 mg/dl our CV is 2.9%. At a level of 325 mg/dl, the CV is 3.5%. Therefore, at a level of 200 mg/dl the possible error is ±12 mg/dl.

High density lipoprotein cholesterol determinations are a greater problem. The CDC data show that for high density lipoprotein cholesterol, the CV at a level of 35 mg/dl is 15%. Therefore, throughout the United States, from laboratory to laboratory, a specimen may yield a value of anywhere from 25 to 45 mg/dl. Again, the data from a single laboratory are much better. In our laboratory, the CV is 5%, which means that in any particular patient, a value of 35 mg/dl has a 95% probability of being reported between 31.5 and 38.5 mg/dl.

Our laboratory has recently begun to receive requests for apoprotein testing. The demand is going to increase, but the accuracy and proficiency data indicate that there are significant problems with the current technology.

Clearly, the way tests are standardized needs to be improved. We need to tighten the criteria for acceptable behavior. While the performance within single laboratories has been acceptable, the need for standardization of our testing methods is evident. Establishing an arbitrary position concerning an acceptable CV is one possibility.

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Discussion

Dr. Grundy (Dallas, Texas): Dr. O'Brien, how should the physician interpret a high density lipoprotein cholesterol value in terms of deciding on a therapy for a patient? Would you recommend that multiple measurements be made before embarking on some particular therapy?

Dr. O'Brien (Teterboro, New Jersey): As a general rule, if the physician is going to initiate therapy that will have a dramatic impact on the patient's life, then it is necessary that a second value be obtained. More than 60% of the time, the range reported will be much better than what I mentioned. But I think it is important that physicians do understand the outside limits of today's precision.

Dr. Rifkind (Bethesda, Maryland): Within limits, one can tolerate a degree of imprecision in the measurement of total cholesterol that one cannot tolerate in the measurement of high density lipoprotein cholesterol. A 5- or 10-mg error in total cholesterol can be accommodated. I do not think it is likely to interfere with the diagnostic process and the levels of risk that are estimated from it, but a corresponding error when you are measuring high density lipoprotein cholesterol, which has a mean of about 45 mg/dl, can give a totally unacceptable range of risk. I think physicians ought to realize that reasonable confidence can be placed in the total cholesterol measurement, but in the area of high density lipoprotein cholesterol, they are susceptible to major errors in assessing a patient.

Dr. Roberts (Bethesda, Maryland): I have 2 questions. First, as I understand it, the Lipid Research Clinics determinations were plasma, not serum, values for total cholesterol and low density lipoprotein cholesterol. What is the difference overall in values obtained from serum versus those obtained from plasma, and which of the two is preferable? Second, I understand that in most studies of systemic hypertension, 3 different blood pressures are taken, and when the level is above a certain number during 2 of those 3 determinations, then the patient is given treatment. I recently examined the chart of a patient who had 20 total cholesterol values determined in the same hospital over a 1-year period. Those 20 values range from 185 to 240 mg/dl. What is the true value of the total cholesterol in that particular patient? Do you average 20 values? How do you handle that type of data?

Dr. O'Brien: I think that within a single facility the range that you describe is too large and unacceptable. I think the patient's value is probably the same in each analysis, and the variation you report is a variation in the behavior of the laboratory. In a situation like that, I think that rather than do something for the patient, we should go to the laboratory and see what is wrong. Regarding serum versus plasma, I always speak from the perspective of someone who is interested in mass screening. We have chosen to do that efficiently on a multichannel analyzer, and to do that we need serum. We did a small study that showed that the difference between serum and plasma was very small and not clinically significant.

Dr. Rifkind: Perhaps I could speak on the serum–plasma differences, as they were systematically evaluated in the Lipid Research Clinics program. We chose plasma, not because we necessarily advocated it as the ideal for the conventional clinical context, but because of the specialized studies that we performed; in particular, for the more detailed analysis of lipoproteins, we had to use EDTA plasma. Because of the dilution effect of the EDTA, plasma provides results that are approximately 2 to 3% lower than serum values. In general, because of convenience considerations and the like, one would expect serum cholesterol to be measured much more often than plasma cholesterol.

Dr. LaRosa (Washington, D.C.): Perhaps it might be worthwhile to emphasize—for those who deal with patients on a day-to-day basis—that besides genetics, diet and the general health of the patient, a multitude of other factors are important in determining the cholesterol level. A patient's cholesterol value can change dramatically in a year. I think because of that there is a need to perform at least a few cholesterol determinations before deciding that a given level is correct for the patient.

Dr. Rifkind: Several speakers have commented on the variations in cholesterol in repeated measurements over time. Some of these changes come from diet, concurrent medications, such as estrogens in women, and intercurrent illness. For example, it is perhaps not well known that cholesterol levels drop dramatically in the weeks after a myocardial infarction. The physician can deal with that problem by standardizing the conditions under which a cholesterol measurement is taken. He should ask that the individual be on the usual diet, be out of the hospital, not take medications that are likely to alter cholesterol levels and that the measurement, as several speakers have indicated, be done on 2 or 3 occasions. Under such circumstances, cholesterol levels are much less likely to vary and reliable interpretation of them is possible.

Dr. Grundy: I have heard that if you are in a standing or sitting position, you will have a higher cholesterol than in a prone position? Is that correct?

Dr. Rifkind: That is correct, and, for example, in the Lipid Research Clinics program, where careful cholesterol measurements on repeated occasions over many years were required, we specified that individuals be recumbent for several minutes and that the tourniquet only be applied for a limited time. Some precautions along these lines ought to be taken in acquiring a sample for cholesterol determination.

Dr. Grundy: It is obviously not possible to do ultracentrifugation in clinical laboratories, which might improve accuracy. We are left, therefore, with having to do an estimate of the low density lipoprotein cholesterol and, to some extent,

of the high density lipoprotein cholesterol. How do the triglyceride levels affect the measurements and what precautions should be taken in patients whose triglyceride levels are high?

Dr. Naito (Cleveland, Ohio): Triglyceride levels can affect the estimation of high density lipoprotein cholesterol and low density lipoprotein cholesterol. If the laboratories do not remove the chylomicrons, if present, by ultracentrifugation, one will get a volume displacement problem. Therefore, your determination of triglycerides will be inaccurate. Second, the Friedewald formula no longer holds in any sample with a triglyceride concentration in excess of 400 mg/dl. At this point, the institution should try and send the sample out to a laboratory where the very low density lipoprotein can be isolated by preparative ultracentrifugation so that a more accurate estimation of the low density lipoprotein cholesterol can be made. In hypertriglyceridemic samples, in which one will have increased pre-β-lipoprotein, interference with the precipitation technique can result, which will cause erroneous values.

Finally, most clinical laboratories throughout the country still do not measure true triglycerides. Rather, they measure total glycerol in the blood and report the values as "triglycerides." If a person does this, one cannot estimate very low density lipoprotein cholesterol by the Friedewald formula because it is based on true triglyceride measurements. This means that low density lipoprotein cholesterol estimations will be inaccurate and unreliable if one doesn't correct for the free glycerol in the blood.

Defining Coronary Risks in a Reference Range for Total Cholesterol and Lipoprotein Values: A Problem Yet To Be Solved

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The *US News and World Report* (February 18, 1985) contained an article entitled, "The English Language: Out to Conquer the World," in which the term "gobbledygook" was defined as that "normally occurring, abnormal occurrence." The authors were referring to the nuclear industry's conception of something that goes wrong all of the time.

In some respects, the problem of defining a level of cholesterol in the blood at which physicians should intervene and treat a patient is directly related to this "normally occurring, abnormal occurrence." In individual prospective studies and from analysis of pooled data from national and international studies, the evidence for an association between coronary atherosclerotic disease and elevated blood cholesterol levels is very strong.[1,2] However, the specific cholesterol level at which physicians should intervene is unclear. This is due in part to the convention of using various reference populations as a basis for reporting laboratory cholesterol ranges.

The important issue is resolution of the dichotomy between the values reported by a clinical laboratory for total serum cholesterol (acceptability defined by reference ranges) and the values associated with increased risk. When should a practicing physician intervene? What effect should knowledge of the high density lipoprotein level have on physician intervention?

Let me first address the question of why it is important to have a denotation of risk. The reliability of laboratory assays is of concern.[3] Unreliability is becoming less of a problem, and, if standardized conditions are used to obtain the blood sample from the patient for determination of lipids, one can assume that reasonable and reliable cholesterol levels are measured. With reliable levels, one can then discriminate between those people who are healthy, and those who are occultly or overtly diseased and require treatment. Treatment for familial or nonfamilial hyperlipidemia should begin with dietary intervention and increase in rigor in accordance with dietary program guidelines such as those of the American Heart Association. Only when dietary modification has been maximized should single or multiple hypolipidemic agents be tried.

An important question that follows is: On which side of the coin does one wish to err? Most authorities now agree that somewhere between 25 and 50% of adult Americans are recorded as false negatives for hypercholesterolemia. On the other hand, virtually no one is being recorded as a false positive for hypercholesterolemia. This is very worrisome because hypercholesterolemia is associated with significant atherosclerotic disease. Overlap of the 2 Gaussian curves developed from the Framingham data for blood cholesterol levels of people who eventually manifest coronary artery disease and those who do not does not diminish the concern.[4] The fact is that people with a false negative classification for hypercholesterolemia are analogous to those with unrecognized systemic hypertension. Both groups are walking time bombs.

It is not the fault of the clinical laboratories that, for the past 30 years, they have used a reference range for defining "acceptable limits" for blood cholesterol. Reference ranges are used for all substances measured in body fluids, including those in blood. Thus, the use of a statistically developed curve to define a population parameter is a traditional laboratory approach. The difficulty is that with cholesterol, the level is not normal in a great number of people. Confusion arises when, for example, a laboratory report is issued with no limiting cholesterol value given to denote increased risk of atherosclerotic disease. Only an upper limit of the reference range is provided, usually between 275 and 330 mg/dl. What the report means is left to the imagination of the clinical physician. When a patient's cholesterol level is 275 mg/dl, which is a level considered high enough to enter people in the Lipid Research Clinics-Coronary Primary Prevention Trial, what is a physician to do when the reference range goes to 330 mg/dl? At a blood cholesterol level of 275 mg/dl, given

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the quintile information from the Framingham study,[4] a person is at a distinctly increased risk for coronary artery disease, yet most laboratories in the United States would not alert the patient or his physician of a need to change the patient's diet.

We recently completed a survey of all academic laboratories in Canada and the U.S.[5,6] We obtained the reference ranges for total serum cholesterol or low density lipoprotein cholesterol, the source of the reference ranges and the level at which these laboratories defined an increased risk. The defined upper limit of "normal" for total blood cholesterol ranged from 220 to 330 mg/dl.

We are left in a bit of a quandry. How can we allow reference ranges to stand as they currently are, given that they represent the populations sampled, while we identify a cholesterol level at which a physician should begin to consider intervention? The evidence for an association between coronary artery disease and certain elevated levels of blood cholesterol is strong enough to suggest that if one exceeds 200 to 220 mg/dl blood cholesterol, overall, one is at increased risk for the development of atherosclerotic disease. Laboratories must find a better method for denoting risk.

The percentage distribution of the major lipoproteins in a total cholesterol measurement must be considered. The high density lipoprotein cholesterol and fasting triglycerides can be used to determine an indirect estimate of low density lipoprotein cholesterol and very low density lipoprotein cholesterol using the Friedewald formula. Then one can make an informed decision about what a total cholesterol level >220 mg/dl means in a given patient. Thus, if a patient has a cholesterol level of 250 mg/dl, but his absolute high density lipoprotein cholesterol value is greater than 75 mg/dl or the percent of high density lipoprotein cholesterol is relatively high, he will no doubt be protected against the development of atherosclerotic disease. On the other hand, a person with a low absolute or relative high density lipoprotein cholesterol but the same total cholesterol level (250 mg/dl) would be at an increased risk. The 2 patients may be managed entirely differently, largely on the inference that low density lipoprotein cholesterol is unhealthily high in 1 patient and not in the other.

The nagging questions about ideal, acceptable, optimal or healthy cholesterol levels are perhaps the most difficult we face in the whole blood lipid–coronary risk matter. In the initial abstracts of the expert panelists of the recent National Institutes of Health Consensus Conference on Lowering Blood Cholesterol, for example, only four ventured an approximation of what the upper limit of a desirable cholesterol level should be. Of course, the consensus statement implied that a total serum cholesterol value of approximately 200 mg/dl is equivalent to mild risk in the young adult, whereas a level >260 mg/dl is equivalent to high risk in people over 40 years of age. Thus, some confusion remains as to what level is the one at which the physician should suggest therapeutic intervention.

The stringency of defining an upper limit of acceptability for total serum cholesterol must be adapted in light of, and applied in appreciation of, the degree of hypercholesterolemia that may exist. People who are far above the limit of acceptability may never be able to obtain a level low enough to fall within the ideal range by reasonable medical intervention. This may be very discouraging to the physician and to patients who are in the high 200 and 300 mg/dl range. The mutual goals of physicians and patients will be different for patients with cholesterol levels in the mid to low 200 range.

It is important to emphasize that the responsibility for transmitting the significance of a lipid value to the patient, whatever that value, is a joint responsibility of the clinical laboratorian and the physician. Neither one can absolve himself of the responsibility to interpret and provide "cholesterol" information. Any interpretation must be done in light of the patient's clinical condition and, especially, in light of all other known quantifiable risks for atherosclerotic disease.

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Defining a Reference Range for Total Cholesterol and Lipoprotein Values

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Physicians should limit themselves to measuring total cholesterol, total triglyceride and high density lipoprotein (HDL) cholesterol levels. Lipoprotein electrophoresis, which is still done by many laboratories, has little clinical utility as a screening device, although it may be useful for detecting chylomicrons and broad β lipoproteins.

There is no universal agreement about the value of HDL cholesterol determinations as a screening device. They are useful, although their reliability in many laboratories is still questionable. HDL subfractions are not as yet of any clinical value. Lipoprotein-apoprotein measurements are of general clinical usefulness, although apoAI and apoB determinations may ultimately be more reliable than HDL cholesterol and low density lipoprotein (LDL) cholesterol determinations.

The normal values for total cholesterol, total triglyceride and HDL cholesterol should be based on some estimate of the associated risk of cardiovascular disease, rather than on means and standard deviations. Although such values are arbitrary, they are no more so than a blood pressure level of 140/90 mm Hg as a measure of hypertension. The precise meaning of such levels will be debated for a long time, but they give the practicing physician some way of dividing patients into those who require therapeutic attention and those who do not.

For total cholesterol, a value of 240 mg/dl is appropriate for delineating associated coronary risk. This is essentially the value that the recent Consensus Conference on Cholesterol recommended for adults as requiring intervention.[1] On the basis of less firm data, an HDL cholesterol of ≤40 mg/dl should be considered as "abnormal".[2] For triglycerides, a level of about 250 mg/dl is "abnormal". That level roughly corresponds to the 95th percentile for middle-aged Americans, and was the level identified by a recent National Institutes of Health Consensus Conference on Triglycerides as requiring intervention.[3]

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As a practical consideration in adults, it is relatively unimportant for the practicing physician to correct these numbers for age or for sex; both risk of cardiovascular disease and cholesterol and triglyceride levels increase with age. When these numbers are applied to children, they are even more likely to identify individuals with substantial metabolic alterations. It should be remembered, however, that plasma lipid levels change dramatically during growth and development, and we must approach therapeutic decisions in children with even greater caution.

The LDL/HDL cholesterol ratio can, of course, be derived from these 3 basic tests and has been promoted as clinically useful. Ratios, however, should be viewed with some skepticism. A patient with elevated total and LDL cholesterol, for example, should not be reassured because the HDL cholesterol is also high. Ratios should never be used in place of the absolute numbers.

LDL cholesterol can be calculated using the Friedewald formula.[4] It must be remembered that this formula is only reliable when the triglyceride is <400 mg/dl. A calculated LDL level is not very useful because it does not provide more information than the total cholesterol level does when HDL and triglyceride levels are known.

Occasionally, persons whose total cholesterol is in the mid-200 mg/dl range will be found to have high HDL cholesterol rather than LDL cholesterol levels. Women taking hormone preparations and those who are athletic will often show elevated HDL cholesterol. These examples provide another reason for measuring HDL cholesterol levels, because it would be inappropriate to intervene in such individuals based simply on the total cholesterol level.

On the other hand, there are people in whom cholesterol levels are normal, triglycerides are normal and HDL cholesterol levels are very low. Most of these people are genetically deficient in HDL cholesterol. They comprise an as yet undefined portion of people with coronary disease who have been characterized as having "no risk factors". In the Lipid Research Clinics Program Prevalence Study, 2 to 3% of adult men had mean HDL cholesterol levels that were <30 mg/dl, even though their total cholesterol and total triglycer-

ides were normal.[5] It must be asked, of course, of what value it is to find such people when we are not at all certain how we should be treating patients with low HDL cholesterol.

It has been proposed by some that persons with low HDL cholesterol be treated with medication that lowers their LDL cholesterol, thus bringing their ratio into better balance, even though their total or LDL cholesterol may not be elevated. There is no evidence at this time that such a regimen is beneficial.

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Discussion

Dr. Gotto (Houston, Texas): I agree with Dr. LaRosa that a level defining what we mean by hypercholesterolemia should be adopted, even though it may be arbitrary. I am perfectly agreeable to using 240 mg/dl as an arbitrary measure for defining moderate risk of hypercholesterolemia. I think it would be a mistake, however, to lose sight of the fact that cholesterol values of less than 240 mg/dl are still potentially dangerous. If one looks at the average cholesterol value of men who have a positive coronary arteriogram or who have coronary artery disease, it is only about 230 mg/dl. This is only marginally higher than the mean in the American population, which is 215 to 220 mg/dl. Therefore, it is important that in defining hyperlipidemia we do not consider a normal value the same as a safe value, because a cholesterol of 220 or 230 mg/dl, in my opinion, is not a safe value.

If one looks at what is considered a low level of high density lipoprotein cholesterol, it is important again to further distinguish between what is considered a normal and a safe total cholesterol. A low high density lipoprotein cholesterol in American society may be much more important than a low value measured in an African or Asian society. What makes a high density lipoprotein cholesterol of 20 or 25 mg/dl dangerous is the fact that the total cholesterol may be 200 or 210 mg/dl, rather than 160 mg/dl. I am not convinced that there is evidence that a low level of high density lipoprotein cholesterol per se is associated with risk if the total levels of cholesterol and low density lipoprotein cholesterol are sufficiently low, as they are in nonindustrialized societies. But in American society, a cholesterol level of 200 mg/dl, which is considered normal, would be too high with a high density lipoprotein cholesterol of 20 mg/dl.

Dr. Roberts (Bethesda, Maryland): It seems to me that the most important issue raised at this conference is determining the normal level of total cholesterol, low density lipoprotein cholesterol and high density lipoprotein cholesterol. It seems to me that the cutoff levels that have been mentioned are those at which cholesterol-reducing therapy should be initiated. We also need a level at which one is going to diminish the risk of coronary disease or arteriosclerosis anywhere in the body, i.e., the level at which coronary disease is preventable. I would say that that level has to be around 150 mg/dl in an adult. If one's level is lower than that, then the chance of getting coronary disease that would be of clinical consequence is virtually nil.

There really should be 4 levels, not just one. I am fully aware that among Americans, only 5% of those over 40 years of age have total cholesterol levels under 150 mg/dl, but this is the group in whom coronary disease is preventable. The second level would be that level at which the risk of getting coronary disease is lowered. The third level would be where diet therapy is initiated to lower the cholesterol and the fourth level would be where drug therapy is initiated in addition to diet therapy.

If we are going to improve the health of this nation, if we are going to prevent coronary disease, it is ridiculous to be satisfied with a cholesterol level of 240 mg/dl. We have got to make that level much lower.

Dr. LaRosa (Washington, D.C.): I do not disagree with either Dr. Gotto or Dr. Roberts. But I still go to community hospitals and talk to physicians who do not treat patients whose cholesterol levels are less than 300, 350 or even 400 mg/dl because we have given them too many levels to deal with. We have given them more information than they can reasonably base a practice on. While we might all consider 240 mg/dl as too high, it is not considered too high by the clinicians who are taking care of patients because of the confusion that has existed in this field and because of the fact that laboratories have traditionally recorded such values as a normal range. I would guess that many practicing physicians would not consider any kind of intervention, even dietary, until the level is 300 mg/dl.

Dr. O'Brien (Teterboro, New Jersey): We will shortly begin to report cholesterol values as a percentile, ranked by age and sex. So the 75th percentile for a 24-year-old man will be 200 mg/dl, and the 75th percentile for a 49-year-old man will be 249 mg/dl.

Dr. McManus (Omaha, Nebraska): Why would you be less likely to be concerned about a middle-aged man with a cholesterol of 220 mg/dl than a 25-year-old man with a cholesterol of 220 mg/dl?

Dr. O'Brien: There is an increase in cholesterol with age, and we assume that it is necessarily a function of disease. There is some change in cholesterol that may be an adaptive mechanism to aging. I would say that a cholesterol value of around 200 mg/dl is more appropriate for a 20- or 25-year-old. But could you reasonably give a cholesterol value of 200 mg/dl as a target for a 59-year-old-man? That might lead to frustration and abandonment of the treatment programs.

Dr. LaRosa: I may end up in the minority, but I don't agree with that approach. I think percentile rankings lead to an unnecessary amount of confusion, and I am becoming less and less convinced that we should make allowances for the so-called "normal" effect of aging.

Risk Criteria

BASIL M. RIFKIND, MD

This article will draw heavily on the recent report of the Consensus Development Conference.[1] One of the questions asked of the members of the conference panel was, did they believe there was a causal relation between cholesterol and coronary artery disease (CAD)? For many of us who have been in the field for many years, this hardly seemed necessary to ask but, given the prior controversy regarding cholesterol and CAD, it was a question that had to be looked at in the light of all the available evidence. The panel unanimously stated that the evidence obtained from genetic, experimental, epidemiologic and clinical investigations, as well as from clinical intervention investigations, overwhelmingly supports a causal relation between blood cholesterol levels and CAD. This is the scientific foundation, drawn from a widely based multidisciplinary approach, upon which the other recommendations of the Consensus Conference are based.

It should be emphasized that the Consensus Conference essentially presented 2 mutually compatible strategies. Review of the available data suggests that levels above 200 to 230 mg/dl are associated with an increased risk of developing premature CAD. It is staggering to realize that this represents more than 50% of the adult population of the United States. I think it is fair to say that this estimate is deliberately conservative. Some argue that a person's blood cholesterol level must be below 150 mg/dl before the risk of CAD is eliminated. In any event, the conference panel agreed that at least 50% of Americans have a significantly increased coronary risk because of high cholesterol levels. Any strategy has to direct attention to this large group, rather than to any subgroup of the population.

The first recommendation of the Consensus Conference was that the entire American public must be encouraged to reduce cholesterol levels; i.e., the curve of the cholesterol distribution must be moved to the left. The panel suggested that the target levels for cholesterol should be about 200 mg/dl for people over 30, and about 180 mg/dl for people under 30. These levels should not be regarded as scientifically precise points. The target levels may actually be lower than this, but the question of practicality was also taken into consideration. The panel wanted to recommend to the entire U.S. population something that can be done at this time. If these recommendations are successful, then consideration could be given to whether new target levels are desirable. The dietary recommendations were to moderate fat intake to about 30% of total energy intake (it is presently about 40%), to reduce saturated fat to ≤10%, to increase polyunsaturated fat, but to no more than 10% and to moderate dietary cholesterol intake to 250 to 300 mg/day. These should be seen as moderate dietary recommendations. Others call for more stringent dietary change. These dietary recommendations are designed to shift the cholesterol levels of the population down toward the target levels.

When defining target levels, we are not defining them for one group and not another. Middle-aged people who fall below the level of 240 mg/dl are often still at increased risk of CAD and the dietary recommendations apply to them, as well. The purpose of target levels is to define a group who require the attention of a rather limited medical resource; we can only apply the one-on-one approach that characterizes conventional medical care to a limited fraction of the population.

Accordingly, the second set of recommendations was directed to that smaller proportion of the population who are at particularly increased risk for CAD. They need intensive physician interaction and counseling from nutritionists, and will have to pay repeated visits before their cholesterol levels are brought under control. In defining the high cholesterol groups, there was unanimity on the panel's part that about 20 to 25% of the population might be defined as at high risk. About 20%, which is the top quintile of the American cholesterol distribution, accounts for about 40% of all myocardial infarctions, which is a substantial number. The other side of that coin is that 60% is accounted for by people below the top quintile, namely the public at large.

The Consensus Conference offered specific recommendations for target levels. Some of the issues that were considered in formulating these recommendations will be briefly discussed. If we want precision in selecting target levels, for example, if we want to take into account age and sex, then a rather complex series

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of levels would evolve, and physicians will not use them. If levels are overly simplified, there is a danger that all the issues will not be addressed, and significant segments of the population will be neglected.

The Conference's compromise is a useful and simple one, and there are indications that it is already being adopted. Their simple tabulation of target levels was rapidly and frequently reproduced in both consumer and professional medical publications.

The Conference defined 2 levels of risk: a group of high-risk subjects, above the ninetieth percentile (the top 10% of the adult population), and a group of moderate-risk subjects, between the seventy-fifth and ninetieth percentile (Table I). The high-risk subjects were, for ages 20 to 29, >220 mg/dl, for ages 30 to 39, >240 mg/dl and for 40 and over, >260 mg/dl. Corresponding levels for the moderate-risk subjects were 20 mg lower in each case; i.e., for ages 20 to 29, 200 mg/dl, for ages 30 to 39, 220 mg/dl and over age 40, 240 mg/dl. These target levels were applied to men and women, again with some sacrifice of accuracy, but with the advantage of practicality.

This is a fairly simple tabulation. It tries to marry simplicity with application, and it does not represent an all-or-none approach. To reiterate, the target levels define a group that needs special attention. Adults aged 30 years or over who fall below the moderate-risk levels, but who are above the target values of 200 mg/dl, still need advice. They still need to bring a cholesterol level of, for example, 230 mg/dl down below the target level.

What shall we do with these levels? The 25% of the population that will ultimately be defined as at high risk is not an inconsiderable burden or challenge to the medical care system. The Conference indicated that, ultimately, all Americans should know their cholesterol levels, just as it is recommended that individuals know their blood pressure and cigarette smoking levels, and do something about them. All Americans should have their cholesterol levels determined. Mass screening in various guises must be instituted eventually. The Conference, however, was justifiably reticent about immediate mass screening. The medical system would be overwhelmed if 50 million Americans were identified as needing one-on-one medical management.

TABLE I **The National Institutes of Health Consensus Recommendation on Total Cholesterol Values for Selecting Adults at Moderate and High Risk Requiring Treatment**

Age (years)	Moderate Risk (75–90th percentile)	High Risk (>90th percentile)
20–29	>200 mg/dl	>220 mg/dl
30–39	>220 mg/dl	>240 mg/dl
≥40	>240 mg/dl	>260 mg/dl

From reference 1.

The Conference Report did note that a high proportion of U.S. adults see their doctors in a given year, and the first approach to screening should be to have a cholesterol determination during a person's first visit to the doctor. Over time, a large proportion of the adult population would then be screened. In the interim, we need to investigate screening approaches and to conduct feasibility studies of how best to screen and how to deal with those individuals that are then identified as being at risk.

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Measurement of Lipoproteins

GERALD R. COOPER, MD, PhD

The issue of which lipoproteins should be measured can best be addressed by asking 2 questions. The first is which lipoproteins should be considered for measurement to provide clinical data? The total cholesterol, which really measures all of the lipoproteins, is a very complex risk factor and cannot stand alone. Triglyceride, which measures very low density lipoproteins, provides information about our triglyceride and intermediary metabolism. High density lipoprotein (HDL) cholesterol is thought to be a risk factor in low concentrations, while low density lipoprotein (LDL) cholesterol is a risk factor in relatively higher concentrations. Intermediate density lipoprotein (IDL) is measured to detect genetic defects; in high concentration it is considered a risk factor. Chylomicrons are remnants and are highly suspected of being involved as a risk factor in the development of atherosclerosis. The most important tests from a clinical standpoint, therefore, are total cholesterol, total triglyceride and HDL cholesterol.

The second question is which lipoproteins should be measured to serve the various functions in the laboratory? The simplest screening test is the total cholesterol determination with observation for turbidity. For a more thorough evaluation, one should measure

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total cholesterol, HDL cholesterol and turbidity. Turbidity is measured because any triglyceride in humans above 250 mg/dl can usually be detected just by observation.

For clinical laboratory evaluation, one must begin with the same assays: total cholesterol, triglyceride, HDL cholesterol and turbidity. This should be followed by determination of cholesterol ratios. In lipid follow-up studies, total cholesterol, triglyceride, HDL cholesterol and chylomicron determinations should be performed. Electrophoresis in follow-up studies can detect any unique proteins, especially IDL hyperlipidemia. In our experience, 95% of type III or IDL hyperlipidemia is detected with the usual electrophoresis and a gel electrophoresis. Apoprotein defects should be considered in follow-up studies; a specimen should be sent to a reference laboratory for IDL, apo-E isoform and C-II tests for genetic determination of type IV hyperlipidemia and other disorders. While there is great potential for apoprotein measurements, there is now a 75% error rate associated with these measurements among laboratories. There are also standardization and interpretation errors. A standardization program is being developed by the International Union of Immunologic Societies, the Centers for Disease Control and the National Institutes of Health.

Another important issue is the timing and frequency of plasma lipoprotein determinations. In cord blood, a total cholesterol can be helpful in identifying suspected cases of hyperlipidemia. In the age group between 3 and 20 years, a total cholesterol and HDL cholesterol should be determined in suspected cases. For all persons between 20 and 40 years, total cholesterol should be measured to detect and prevent disease. In persons between 40 and 60 years, it is important to remeasure lipids to evaluate the effects of aging.

The frequency of analyses may vary. For example, HDL cholesterol is a constant measurement in a person unless changes in life-style occur. To monitor changes of the powerful causal agent—LDL cholesterol—we must follow with a test of total cholesterol because as long as conditions are controlled, the total cholesterol will reflect changes in the LDL cholesterol.

Discussion

Dr. McManus (Omaha, Nebraska): I would like to underscore what Dr. Cooper is saying about obtaining a reliable cholesterol value. Multiple values at different points in life may be useful for different purposes in the management of patients, but I think we all are aware that there are many patients today who do not have a single cholesterol determination in the clinic or hospital record, and yet they may have been hospitalized numerous times. Considering the low cost of a total cholesterol assay relative to other types of tests, and accepting its limitations, I think that having at least a single total cholesterol at some time during adult life is nearly mandatory for proper follow-up of all patients.

I have a question for Dr. Gotto. As an advocate of a single range for cholesterol values—that is neither sex- nor age-related—for simplicity's sake, I am confused about the significance of the aging curves in serum cholesterol. I think this is similar to the way in which "essential" hypertension received this designation; that is, blood pressure was "supposed to" rise as a normal aging phenomenon in our population. Total cholesterol is now also expected to rise with age. What, if anything, does decreased capacity of liver receptors like the low density lipoprotein receptor in an otherwise nondiseased liver have to do with this phenomenon? Is receptor activity a major determinant, or is it something to do with absorption of cholesterol, or do we know? Is this something we should be isolating in efforts to understand the pathobiologic significance of the aging curve?

Dr. Gotto (Houston, Texas): We do not know why the cholesterol level increases with age. We don't really know the role of diet in this, and we do not know how much cholesterol rises with age in nonindustrialized societies after adolescence. In all societies cholesterol increases with age, up until early adulthood. In Western society, cholesterol continues to increase, at least up to age 65. It is certainly possible that a high-fat diet over a long period of time could suppress the level of low density lipoprotein receptors in the liver and as a result contribute to this rise in low density lipoprotein and total cholesterol, but I would have to emphasize that it is speculative at this point.

In terms of relative risk, I think there is no question that the relative risk increases as the cholesterol increases with age. We can divide relative risk on the basis of percentile values of cholesterol. On the other hand, we probably should not feel more secure with a cholesterol of 240 mg/dl at age 50 years than we should at age 20 years. At age 20 years, it just represents that much more of a risk than it does at age 50.

I wanted to ask Dr. Cooper a question. I understood you to say that levels of high density lipoprotein and of triglyceride, if measured under basal conditions, do not vary that much. My comment is that patients usually are not in the same state when they come back to visit the physician. We have done measurements in persons who have been put on exercise programs, for example, and we have found that over a period of a year the high density lipoprotein cholesterol may go from 40 mg/dl to 80 to 100 mg/dl, in some cases with prolonged periods of physician training and individual exercise. Unfortunately, within a week or 2 after stopping the exercise, the high density lipoprotein goes back down. In clinical practice, triglycercide is very variable. The patient may lose or gain a few pounds and the fasting triglyceride varies quite remarkably. In terms of actual clinical practice, therefore, while there is less variation of high density lipoprotein, triglycerides vary quite widely from one patient visit to another, unless there is some change in physical activity, alcohol consumption or intake of a new drug.

Dr. Cooper (Atlanta, Georgia): If you are monitoring therapy in a patient who does not have a fairly constant lifestyle, then I agree you have to really use a battery of tests.

Dr. Grundy (Dallas, Texas): How often should a person have cholesterol measured?

Dr. Roberts (Bethesda, Maryland): It seems to me that everyone who is admitted to a hospital in this country today should have at least a total cholesterol test. Although the hospital may not be the best place to do this, we never know the cholesterol level of most patients who are seen in my pathology laboratory who have had fatal coronary disease. It is really the exception to know.

Dr. Rifkind (Bethesda, Maryland): We know that only a handful of Americans know their cholesterol level. It is important to take the same approach to cholesterol that has been so successfully taken with blood pressure. Adults should have a cholesterol check and if the cholesterol is normal then it might be repeated at 5-year intervals. If it is abnormal, obviously the situation changes. The data that were used in the Consensus Conference were from the National Survey of Health Statistics, which indicated that a majority of American adults see their physicians at least once a year. If at these visits, a routine sample was taken—it need not be a fasting sample—then most Americans would soon know their cholesterol levels.

Dr. Grundy: Dr. Gotto, what are some simple, rapid methods of measurement that may facilitate the cholesterol screening process?

Dr. Gotto: I am aware of 3 companies that are currently working on methods for measuring cholesterol from a finger prick. This measurement can be carried out in 2 to 3 minutes, and does not require a venipuncture. The methods are based on enzymatic measurement of cholesterol, and they appear to have a good degree of precision and accuracy. The cost is expected to be $1 or less. With the development of this technology for measuring cholesterol, it is conceivable that screening could be done on a massive basis at work, school, shopping centers and airports.

Interpreting Lipid Values from the Clinical Perspective

ANTONIO M. GOTTO, Jr., MD, PhD

Lipid tests have to be interpreted on an individual basis by the patient's physician. The physician will want to take into account the family history, the physical examination and other laboratory tests. In making a diagnosis of primary hyperlipidemia, the physician has to exclude secondary causes of hypercholesterolemia or hyperlipidemia, to make sure that the patient does not have underlying nephrosis, liver disease, hypothyroidism or some other secondary problem. If the patient has primary hyperlipidemia, the next question is whether or not this is a familial type or other recognized hyperlipidemia, or a sporadic hyperlipidemia. Hypercholesterolemia may be of genetic basis, but not necessarily one of the commonly encountered hyperlipidemias, such as familial hypercholesterolemia. Over 90% of patients with hypercholesterolemia fall in the category of sporadic or polygenic etiology.

Another important consideration is the presence of given risk factors. The significance of a cholesterol level of 200 mg/dl depends on whether or not a person smokes cigarettes, has hypertension or has diabetes. A cholesterol level of 200 mg/dl in a diabetic patient who has hypertension and smokes is of much greater significance than a cholesterol of 200 mg/dl in a person who has none of the other risk factors.

The physician then has to decide whether or not a given level of cholesterol is too high, and, taking this and other clinical information into account, whether or not to begin treatment. If the cholesterol level is above moderate risk (>200 to 240 mg/dl), then the physician should undertake treatment. Treatment should begin with diet and, if the cholesterol level still remains elevated above the high risk level, drug therapy should definitely be added to diet therapy.

We also need to distinguish between those persons who are at high risk for coronary disease (on the basis of hypercholesterolemia and hyperlipidemia) and the general population. By high risk, I mean those persons at the upper end of the range of cholesterol levels. As far as the rest of the population is concerned, I agree with the position of the American Heart Association and the recommendation of the Cholesterol Consensus Conference Panel (see the article by Rifkind in this issue). That is, I believe the whole population needs to go on a diet with less fat, less saturated fat and less cholesterol to reduce cholesterol levels across the board. The American Heart Association has recommended that such a diet should be begun in everyone after the age of 2, and I agree with that general approach (Table I).

It is useful in terms of the overall population to consider the average level of cholesterol as it now exists, the ideal level of cholesterol and a feasible level of cholesterol. The average cholesterol level in the American population is about 215 to 220 mg/dl. The ideal level is ≤160 mg/dl. A feasible level would be approximately 190 mg/dl; this could be achieved if we could persuade the American population to go on phase 1 of the American Heart Association diet. In order to achieve these levels in adults, we have to intervene in childhood. If we strive to have an average cholesterol level of 180 to 190 mg/dl in adults, it is necessary to achieve an average cholesterol level of 160 mg/dl in children. Prevention across the board should be begun in childhood, after age 2, to achieve these objectives.

TABLE I Cholesterol-Lowering Diet with 3 Phases of Fat and Cholesterol Restriction

Phase	1	2	3
Fat (% calories)	30	25	20
Carbohydrate (% calories)	55	60	65
Protein (% calories)	15	15	15
Cholesterol (mg)	300	200–250	100–150
P/S (ratio polyunsaturated fat to saturated fat)	1	1	1–2

Adapted from the American Heart Association Special Report. Recommendations for treatment of hyperlipidemia in adults. Circulation 1984;69:suppl:1065A–1090A.

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Interpreting Lipid Values in the Laboratory

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Useful laboratory interpretation depends on 3 factors: a valid sample, an accurate method and a specific interpretation. A valid sample may be affected by a number of conditions. For example, precollection conditions are important. Among the circumstances that influence the precollection condition are the patient's life-style, diet, exercise and medication, especially diuretics. Intercurrent illness can also alter a patient's lipid levels; e.g., cholesterol levels drop dramatically in the weeks after a myocardial infarction.

Several factors that influence collection conditions deserve consideration. For example, if a person is recumbent for 20 minutes before a sample is taken, there can be a 15% change in the cholesterol value. If the tourniquet is applied too tightly for longer than 2 minutes, a change of 2 to 10% in the value can result. In addition, the anticoagulant used in the vacuum container can dramatically affect the sample. Heparin does not cause any difference between plasma or serum; however, versene causes a 3 to 5% difference. Oxalate creates an 8% difference, and citrate and fluoride can cause changes of as much as 12 and 18%, respectively. When using plasma, a full tube should always be collected. The source of the blood also affects the cholesterol level; there are differences between arterial and venous blood.

With regard to laboratory conditions, the measurement will be affected by the handling, storage and shipment of the specimen. In addition, the laboratory should have stable material with which to perform its analysis.

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The enzymatic cholesterol and triglyceride methods are now widely used, accurate methods. Concern about incomplete hydrolysis, however, still exists. Complete hydrolysis must occur and results of the enzymatic method must agree with those of reference methods that yield true values. There are also problems involved in performing enzymatic triglyceride determinations. Correction for free glycerol is perhaps even more important. With respect to high density lipoprotein cholesterol methods, we must accept the fact that all the separation techniques yield different results in both high and low concentration specimens. I advise selecting 1 method, learning its problems and then specifically interpreting the results with respect to observed reference concentration and ratio ranges.

Finally, it is essential to develop specific interpretations to keep up with the development of accurate analytical methods. For the most part, laboratories and clinicians are not making sufficient use of the highly sophisticated methodology available. It is no longer acceptable to simply tell a patient that he is within a nonsensitive total cholesterol expected range of 150 to 250 mg/dl. Further, it would be helpful to the clinician if the laboratory could provide a percentile value that is normal to the observed population, as well as the absolute concentration value, of each patient's cholesterol determination.

In conclusion, there are 2 demands that must be made to ensure accurate test results. First, the clinician should demand that the laboratory give him an accurate result. Second, the laboratory director should demand that industry give laboratories reference materials, particularly calibration materials, that have been labeled accurately with reference methodologies. Together, these will do much to enhance the reliability of laboratory testing.

Discussion

Dr. Rifkind (Bethesda, Maryland): Dr. Gotto, you have stated that the dietary recommendations to the American people should be applied down to age 2, and that is not consistent with the recommendations of the American Heart Association and of the Consensus Conference. Earlier on, someone mentioned that reservations have been expressed about such dietary change in children. How do you respond to the criticisms that you have had regarding dietary fat restriction in childhood?

Dr. Gotto (Houston, Texas): I know of no evidence that the type of diet that we are talking about—30% calories of fat, 10% saturated, 10% polyunsaturated, 10% monounsaturated, with 250 to 300 mg of cholesterol and a balanced overall diet—is harmful to children or to adults. I think it is important to emphasize the fact that we are talking about a well-rounded, nutritious diet. The average person and many physicians think that we are talking about a very restricted diet. We are not. It is not impossible to provide such a diet—one with balanced meals, and food that is tasty and healthy at the same time. There are 2 reasons for starting such a diet as this: one is established and the other is theoretical. The established fact is that changing the dietary habits of the American population begins with children.

The second reason, the theoretical one, is that if we start such a diet earlier in life, we can possibly avoid the changes that occur by the time a person is 25 or 30 years old in our society, when some degree of coronary lesions can be detected. This has not been established experimentally, but I think at least it is a theoretical basis for adopting a diet.

Dr. LaRosa (Washington, D.C.): Dr. Gotto, you mentioned that relatively early in patient evaluation you would want to establish whether or not the patient has a genetic abnormality. For most practicing physicians, whose laboratory access may be limited to their local community or to a standard laboratory measurement, that sort of workup is either difficult or impossible. Is it important enough that such patients be referred somewhere else for evaluation? Do you feel that given our relatively limited ability, in terms of dietary and drug interventions, it is worth it to do that?

Dr. Gotto: I believe it is important to establish the lipoprotein type and whether the lipid disorder is familial, particularly the upper fifth percentile, where there is a much greater likelihood of identifying one of the well-recognized genetic forms of hyperlipidemia. For the group with cholesterol values in the upper twenty-fifth but below the fifth percentile, I think there is also some value in the work-up. For example, individuals affected with familial combined hyperlipidemia or familial multiple-lipoprotein-type hyperlipidemia may have only moderate elevations of cholesterol or triglyceride but have a greatly increased risk for early coronary disease.

When to refer a patient to a specialized center depends on the individual physician's confidence in the local laboratory, on his experience in dealing with these disorders and, to some extent, on his success. If he is able to put a patient on a diet and, if necessary, to start medication, and he gets a good response, then he does not need to refer the patient elsewhere. If on the other hand, he is unsuccessful, he may wish to consider referring the patient to a specialist.

While we have several drugs currently available, we would like to have a safe, effective agent that will lower total cholesterol and low density lipoprotein cholesterol by 50%.

Dr. Grundy (Dallas, Texas): Dr. Cooper, there have been some investigators who have suggested that if we could accurately measure the apoproteins we would have better indicators of risk. What is your judgment about that?

Dr. Cooper (Atlanta, Georgia): I think the potential for apoprotein measurements is great, but at the present time, the surveys indicate that a 75% error of measurements occurs between laboratories. There are problems of standardization and interpretation.

Dr. McManus (Omaha, Nebraska): I wanted to come back to Dr. Cooper's comments about reliability of lipid assays. We surveyed 121 academic clinical laboratories on questions pertinent to cholesterol. They were asked where they obtained their reference ranges for total serum cholesterol. The results highlight a fundamental problem that still exists with our best general blood test for coronary risk—total serum cholesterol. Even though there is substantial reference information available from the Centers for Disease Control and elsewhere, we found that of the 121 laboratories reporting, 17 based their reference range for cholesterol on a "local population", 15 on "healthy" people, 13 on a textbook, 12 on "unknown" publications, 10 on "manufacturers' inserts", 9 on "unspecified" patients and others on obscure bases, including venerable opinion. Two laboratories did not know where they obtained their cholesterol ranges. Thirty-seven laboratories did cite sources for reference ranges from published reports. I think these simple data pinpoint a problem in standardization.

A second message from the study is that of all the laboratories reporting, only 13 reported some kind of cutoff for total cholesterol values above which coronary risk was increased, 7 reported risk levels based on a total "lipid profile", 9 for a ratio of total cholesterol/high density lipoprotein cholesterol and another 6 for high density lipoprotein cholesterol alone. Three did it "informally"; i.e., the clinical laboratories contacted the clinical physician if the cholesterol value was considered too high. Finally, 3 laboratories said it was "the doctor's problem." I think there are very simple but pervasive information problems that need our attention in the attempts to better standardize laboratory reporting of lipid results.

Conclusions

SCOTT M. GRUNDY, MD, PhD

In recent years, several important advances have been made in the laboratory measurement of plasma lipids and lipoproteins. Perhaps the most important has been the introduction of enzymatic methods for the quantification of cholesterol and triglycerides. This approach has the potential for making highly precise measurements. The use of automated procedures combined with enzymatic measurements allows for the rapid processing of large numbers of samples. This capability provides a base for the broad screening of many patients for plasma lipids at a reasonable cost, and thus affords the opportunity for an active prevention program for the American population.

While total cholesterol measurements provide a good assessment of risk, laboratories must be able to accurately measure individual lipoproteins, including high density lipoprotein (HDL), low density lipoprotein and triglycerides. The accurate measurement of HDL cholesterol is particularly important. This measurement is needed to quantify cholesterol in the other lipoprotein fractions, and it also is needed to obtain an accurate estimate of total cholesterol/HDL cholesterol ratio. One of the major weaknesses of lipoprotein determinations in laboratories throughout the country appears to be in the measurement of HDL cholesterol. Different methodologies are used, and quality control needs to be improved.

This symposium considered reference ranges that should be used for total cholesterol and triglycerides in the American population. There was general agreement that the values outlined by the Consensus Conference on Lowering Blood Cholesterol to Prevent Heart Disease are reasonable. Table I provides a summary of the conclusions of the symposium with regard to risk categories for total cholesterol.

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In evaluating patients with hyperlipidemia, it is important to simultaneously search for other risk factors—such as smoking, hypertension, diabetes mellitus and obesity. All of these factors significantly enhance the risk associated with any given level of cholesterol. For example, the risk for coronary artery disease (CAD) in a nonsmoker with a cholesterol level of 240 mg/dl is about twice that of a person with a baseline level of 200 mg/dl. In a smoker, in contrast, the risk is increased 4- to 6-fold above baseline. Thus, without the knowledge of other risk factors, an accurate assessment of the impact of plasma lipids and lipoproteins on coronary risk is not possible. All of these other factors accentuate the risk, and they heighten the importance of the plasma lipids and lipoproteins as risk factors for CAD.

Physicians who care for patients must learn how to interpret tests correctly, make clinical judgments about their patients and apply appropriate treatment on the basis of their findings, whether this treatment be the use of diets or drugs. We are very encouraged by the fact that there is a decline in the rates of CAD; careful analysis of this decline indicates that it is due in large part to modification of risk factors, including lowering of cholesterol, decrease in smoking and control of other risk factors in the U.S. population.

TABLE I Risk Categories Based on Plasma Total Cholesterol Levels

Risk Category	Plasma Cholesterol (middle-aged adults)	Population Percentile
Desirable range	<200 mg/dl	<40th
Mildly increased risk	200–240 mg/dl	40–75th
Moderately increased risk	240–265 mg/dl	75–95th
High risk	>265 mg/dl	>95th

The actual levels of plasma cholesterol shown are for middle-aged adults; the same percentiles hold for young adults, but the concentrations are lower.